EXHIBIT A

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Klint et al.

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(54) **NEEDLE MOUNTING SYSTEM AND A METHOD FOR MOUNTING A NEEDLE ASSEMBLY**

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Related U.S. Application Data

(62) Division of application No. 12/770,317, filed on Apr. 29, 2010, now Pat. No. 8,137,325, which is a division of application No. 11/778,274, filed on Jul. 16, 2007, now Pat. No. 7,762,994, which is a division of application No. 10/609,744, filed on Jun. 30, 2003, now Pat. No. 7,654,986.

(60) Provisional application No. 60/394,083, filed on Jul. 3, 2002.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A61M 5/00 (2006.01)

(52) **U.S. Cl.**
USPC **604/240**; 604/241; 604/242; 604/243

(58) **Field of Classification Search**
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See application file for complete search history.

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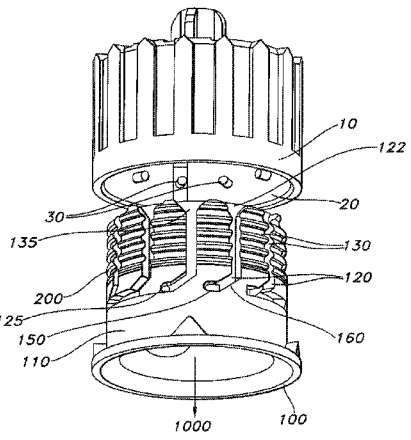
(57) **ABSTRACT**

A needle mounting system and methods for mounting a needle assembly on a needle mount are disclosed. The needle mounting system includes a needle hub having protrusions extending radially inward. A needle mount has a plurality of slots to receive the protrusions. The slots have a first portion that defines a passageway substantially parallel to a longitudinal axis of the needle mount and a second portion substantially perpendicular to the axis. The needle hub and mount provide a method wherein a needle assembly may be mounted on an injection device without completely rotating the needle hub relative to the needle mount.

6 Claims, 8 Drawing Sheets



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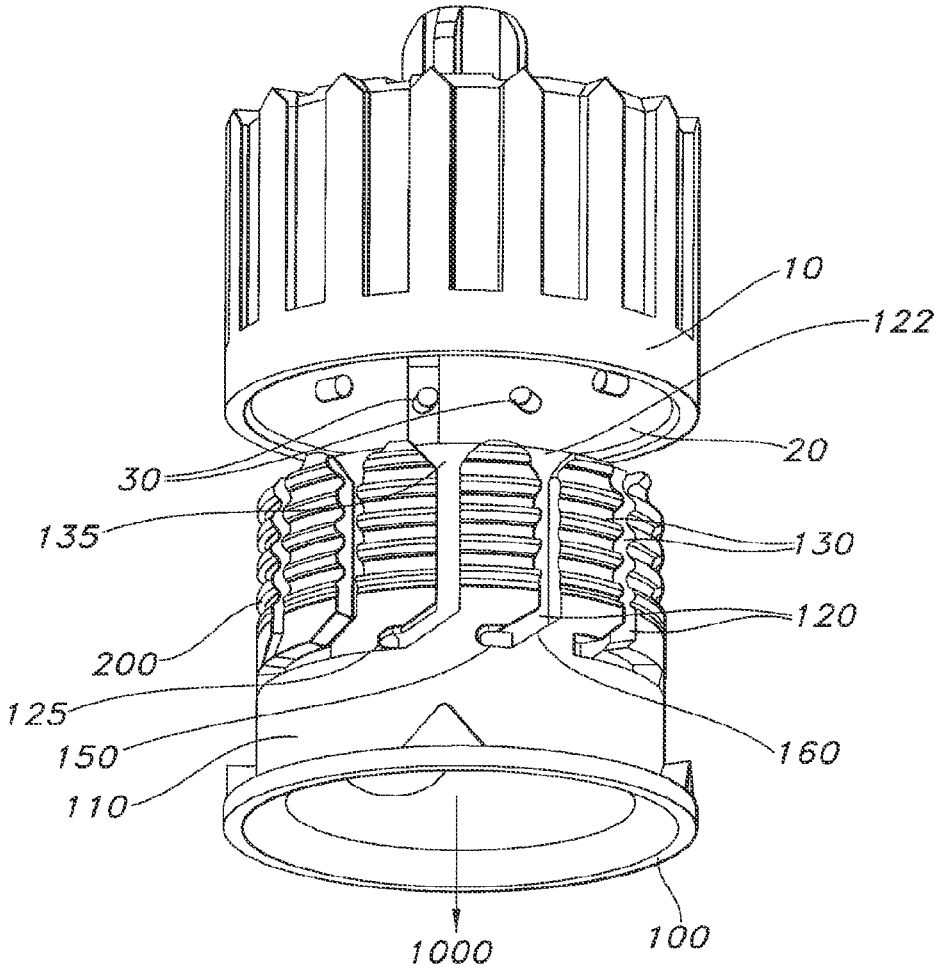

FIG. 1

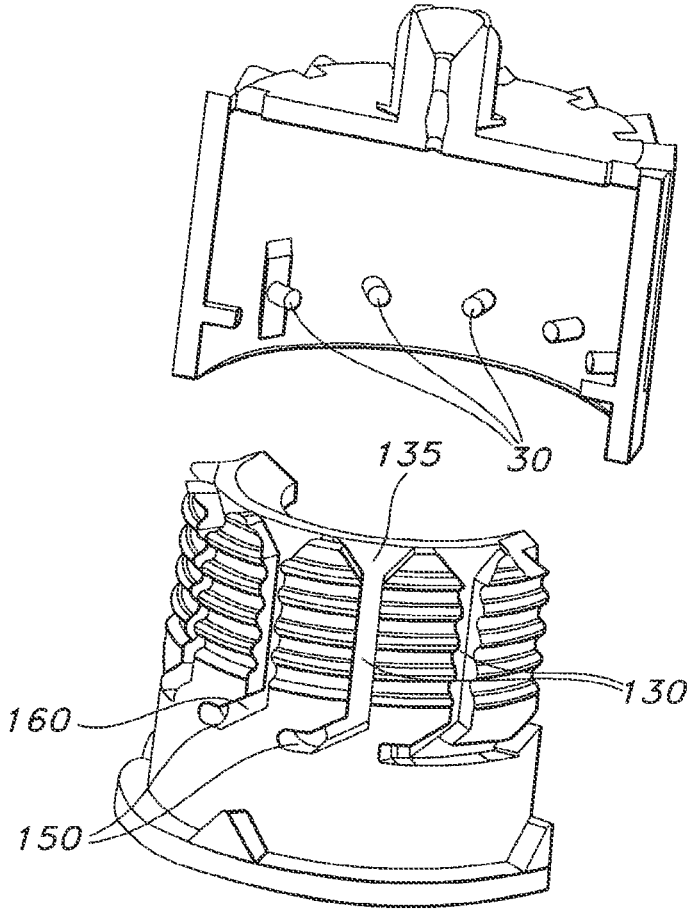

FIG. 2

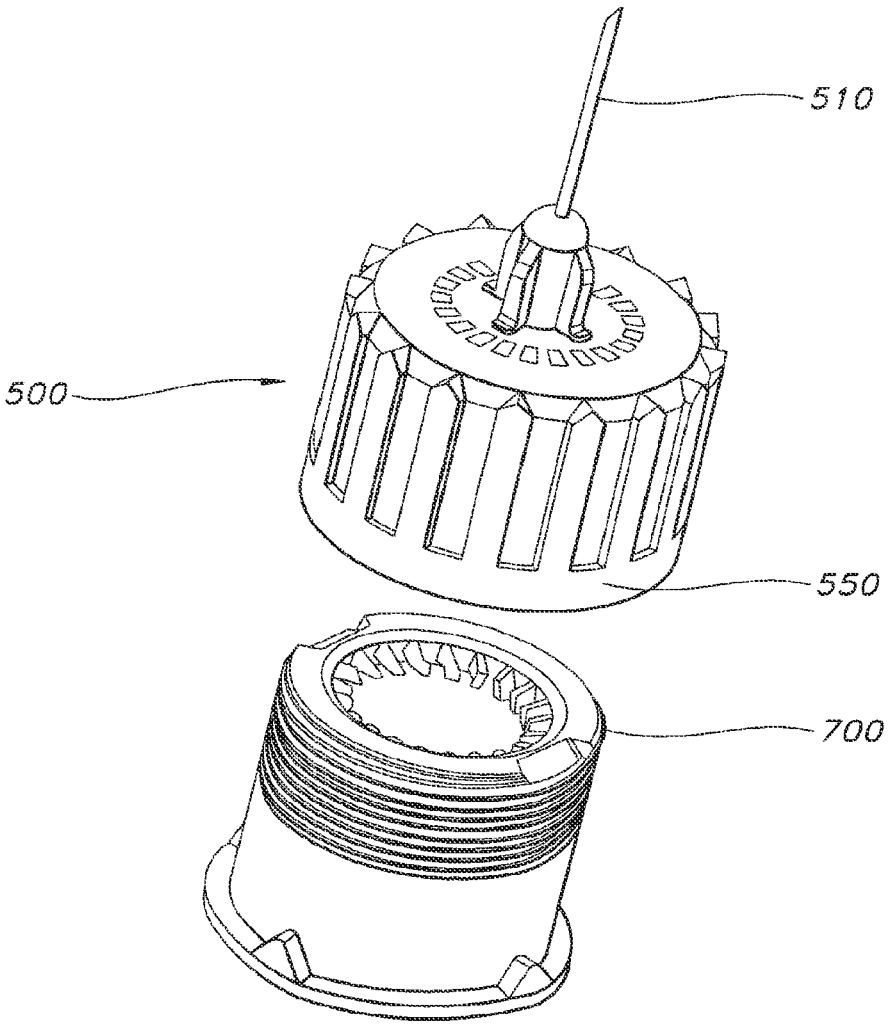

FIG. 3

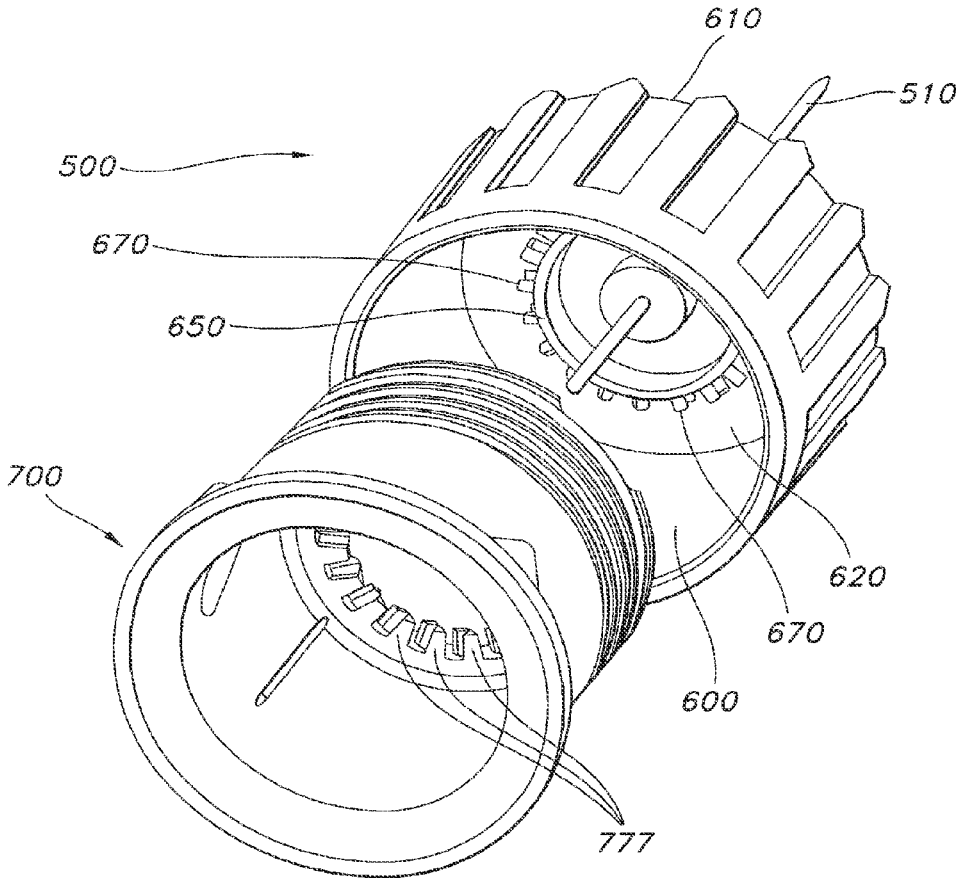

FIG. 4

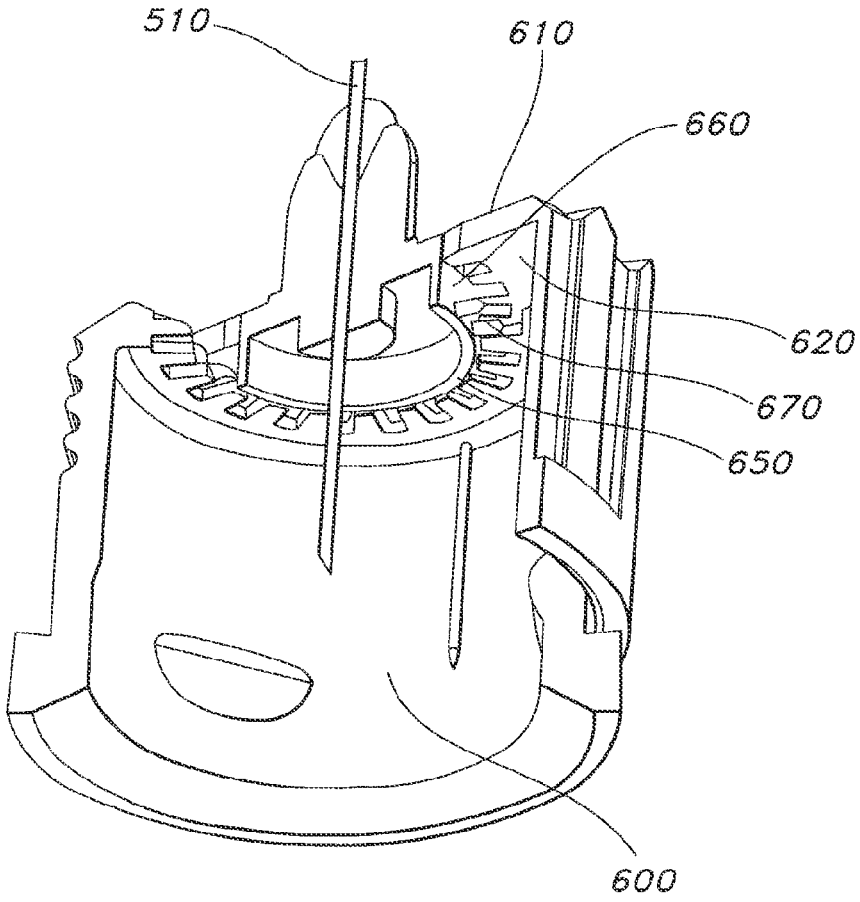

FIG. 5

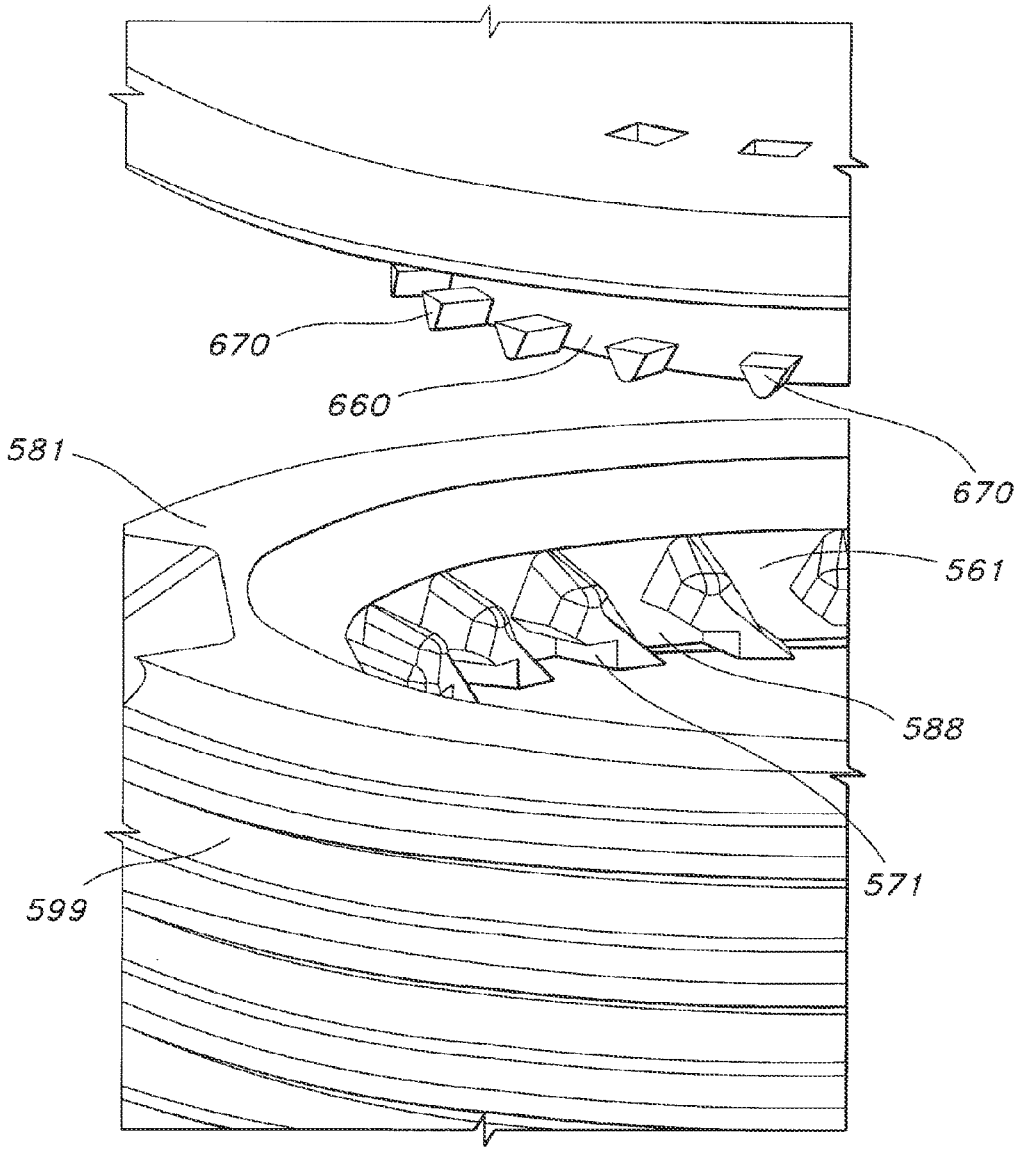

FIG. 6

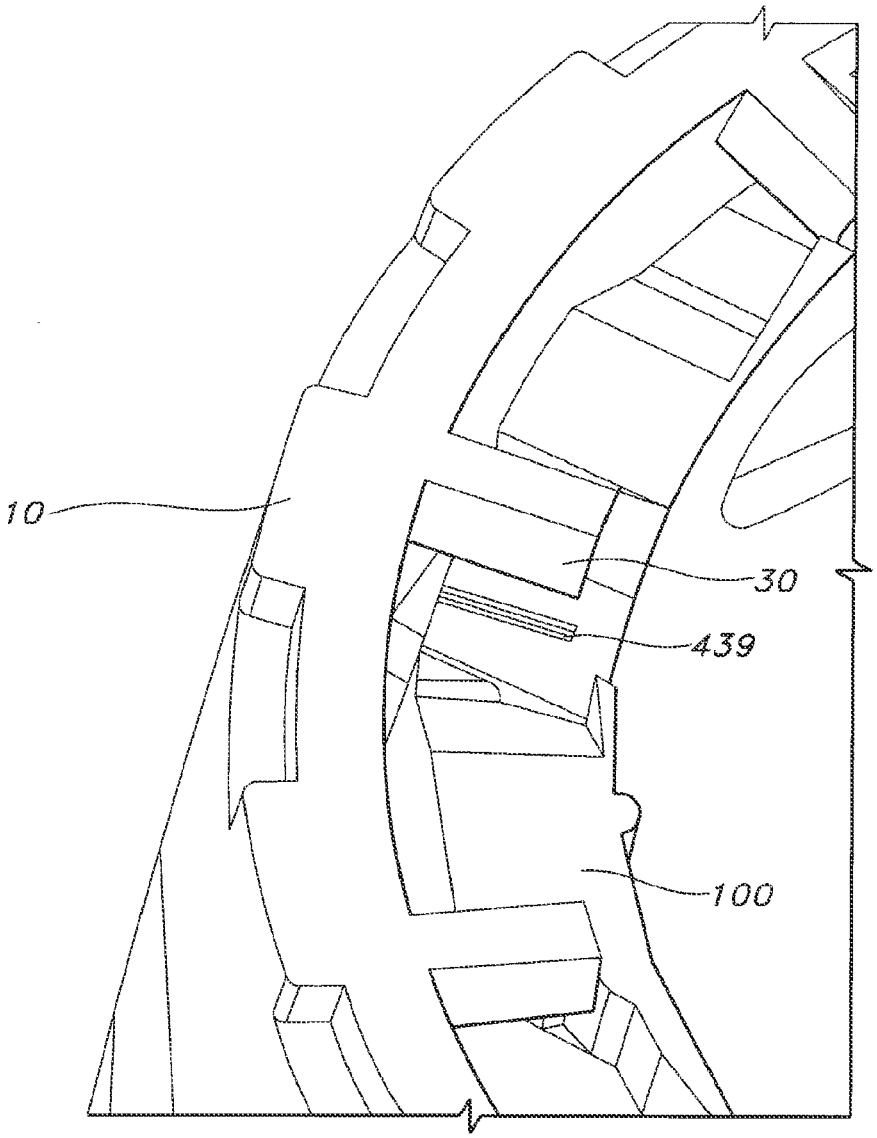

FIG. 7

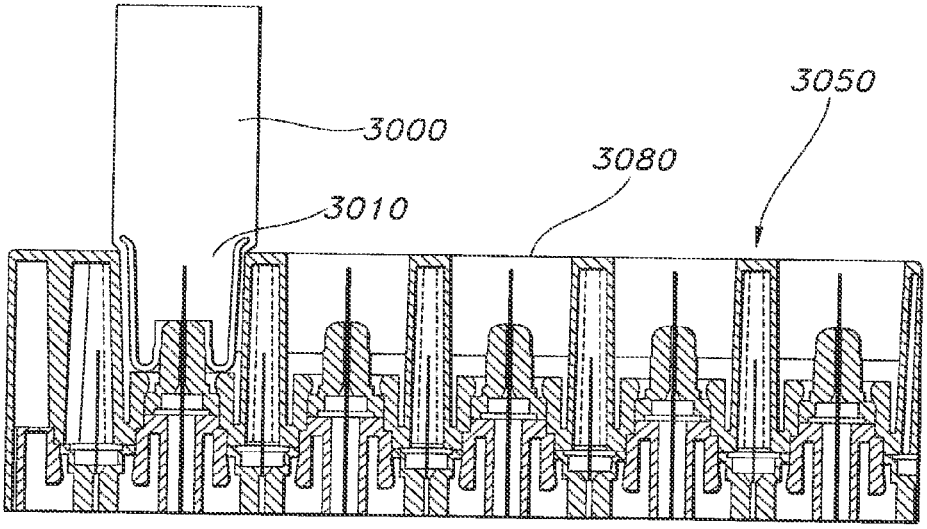

FIG. 8

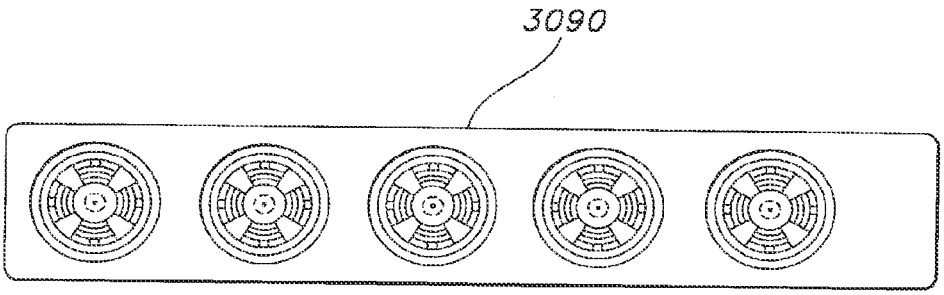

FIG. 9

NEEDLE MOUNTING SYSTEM AND A METHOD FOR MOUNTING A NEEDLE ASSEMBLY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. application Ser. No. 12/770,317 filed Apr. 29, 2010, now U.S. Pat. No. 8,137,325, which is a divisional application of U.S. application Ser. No. 11/778,274, filed on Jul. 16, 2007, now U.S. Pat. No. 7,762,994, which is a divisional application of U.S. application Ser. No. 10/609,744 filed on Jun. 30, 2003, now U.S. Pat. No. 7,654,986, which claims priority under 35 U.S.C. 119 of Danish application no. PA 2002 01169 filed Aug. 1, 2002, and U.S. provisional application No. 60/394,083 filed Jul. 3, 2002, the contents of which are fully incorporated herein by reference.

THE TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to injection devices and, in particular, provides methods and systems for mounting a needle to an injection device or to an ampoule that my be mounted in the injection device.

DESCRIPTION OF RELATED ART

Injection devices, also referred to as dosers, have greatly improved the lives of patients who must self-administer drugs and biological agents. Dosers may take many forms, including simple disposable devices that are little more than an ampoule with an injection means or they may be highly sophisticated instruments with numerous functions. Regardless of their form, they have proven to be great aids in assisting patients to self-administer injectable drugs and biological agents. They also greatly assist care givers in administering injectable medicines to those incapable of performing self-injections.

In particular, pen-style injection devices, have proven to be an accurate, convenient, and often discrete, way to administer drugs and biological agents, such as insulin. Modern devices have become more sophisticated and often include diverse and robust functions, such as memories for remembering time and amount of last dose, as well as, in the case of insulin devices, blood glucose monitors. While pen-style dosers are typically cylindrically shaped with needles protruding from the most distal portion of one end of the device, some of the more modern and for sophisticated dosers have other shapes with the needle no longer protruding from the most distal part of an end of the device. (See e.g., Innovo® and InnoLet® from Novo Nordisk A/S Bagsvaerd Denmark).

Typically, injection devices use a pre-filled cartridge containing the medication of interest. The cartridge may be an integral part of the doser or it may comprise an ampoule having a membrane at one. See U.S. Pat. No. 6,312,413 to Jensen et. al, which is hereby incorporated by reference. Often the end of the ampoule having the membrane is fitted with a needle mount. The needle mount usually comprises a threaded mounting surface to allow a needle assembly, such as a needle and hub assembly, to be screwed on.

The needle mount may be an integral part of the ampoule or may be a separate adapter top (see U.S. Pat. Nos. 5,693,027 and 6,126,646, which are hereby incorporated by reference) that is mounted to the ampoule. Of course, some dosers have needle mounts that are integral parts of the closer.

In the typical injection device where the needle mount is not part of the doser, the end of the ampoule having the needle mount protrudes from the injection device. Where the needle mount is part of the doser, the needle mount is usually disposed on an outer end of the doser. In either embodiment, the needle hub is then screwed onto the needle mount. One disadvantage of the prior art needle mounting systems is that they require the patient to screw the needle hub onto the end of the ampoule, or the doser, by turning the needle relative to the device several times. For patients with dexterity problems, this is inconvenient. Moreover, it is often desirable to store needles for the injection devices in a magazine. Often many newer generation injection devices are not cylindrical and in many new devices, other parts of the device extend past the needle mount making it impossible to mount the needle on the injection device without first removing it from the magazine.

SUMMARY OF THE INVENTION

The present invention provides systems and methods for mounting needle assemblies to injection devices and/or ampoules. In some, but not necessarily all embodiments, the system and method of the present invention allows a needle and hub assembly to be mounted on an ampoule and/or injection device without having to rotate completely the needle hub assembly relative to the injection device. In one embodiment of the present invention, a needle assembly is comprised of a needle mounted in a hub. The needle assembly also includes a means for mounting the hub to a needle mount with only a partial rotation of the needle hub relative to the mount. In an other embodiment of the present invention, a needle mount for mounting the needle assembly is comprised of an outer wall and a mounting means for affixing the needle assembly to a top end of the outer wall. In some embodiments, the means provides for completely securing the needle assembly to the needle mount with only a partial rotation of the needle mount. In some embodiments, the needle mount includes a means for aligning the needle assembly on the mounting means. The needle mount and needle assemblies of the present invention, when combined, make up a needle mounting system. The system, or its components, may also include a means for tactilely or audibly determining when the needle assembly is securely mounted on the needle mount.

At least one embodiment of the present invention includes a needle assembly that is comprised of a needle mounted to a hub having an interior wall. In this embodiment, a plurality of protrusions extends radially inward from the wall of the hub. Typically, the hub wall is cylindrical. A needle mount for use with the present invention, may in at least one embodiment, include a structure having a cylindrical outer wall. A plurality of grooves is disposed on the outer wall. The grooves begin at the top of the wall and contain at least two portions: a first portion that defines a passageway that is substantially parallel to the cylindrical axis of the outer wall, and a second portion that is oriented at an angle to the first portion. Of course, the present invention may be embodied in structures wherein the grooves are disposed inside the hub of the needle mount and the protrusions are disposed on an outer surface of the needle mount.

In at least one embodiment of the present invention, the needle assembly is completely mounted on an injection device with only a partial rotation of the needle assembly relative to the injection device. (Those skilled in the art will recognize that rotation of the needle assembly relative to the injection device may be accomplished by holding the device stationary and rotating the needle assembly or by holding the needle assembly stationary and rotating the device or by a

combination of these steps). In some embodiments, the needle is mounted on an ampoule that is mounted in the injection device.

The present invention therefore provides a method for mounting needles to injection devices. The method may be useful in mounting needles stored in magazines and is particularly useful for injection devices that have a portion that extends past the needle mount. In one embodiment, the injection device is partially inserted into a magazine holding needle assemblies. The injection device is rotated relative to the magazine by less than a full revolution and is then removed with the needle assembly attached thereto. In some embodiments no or minimal rotation is required.

In other embodiments of the present invention, the needle assembly may include a cylindrical hub that has a needle mounted thereon. The hub may have an internal cylindrical element with an outside cylindrical wall that faces the hub's inside cylindrical wall. A plurality of protrusions may extend radially outward from the internal cylindrical element, A corresponding needle mount may be used. The needle mount, in one embodiment, may include a plurality of locking elements arranged on an interior cylindrical surface (e.g., a wall) of the needle mount to form first passageways that are substantially parallel to the cylindrical axis of the needle hub. In some embodiments, the locking elements are disposed on a ring that is part of the interior surface or that is attached to, or part of, an inside wall of the needle mount.

Further the protrusions could be sized to fit between threads of a standard ampoule adapter top. The protrusions arranged on the inner hub wall and aligned between the threads of a standard adapter top would allow the needle assembly to be screwed onto the adapter top in a traditional manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a three-dimensional view of a needle hub and needle mount according to one embodiment of the present invention.

FIG. **2** is a cut-away view of the needle mount and needle hub shown in FIG. **1**.

FIG. **3** is a three-dimensional view of a needle assembly and needle mount according to a second embodiment of the present invention.

FIG. **4** illustrates the embodiment of FIG. **3** when viewed from below.

FIG. **5** is a cut-way view of the needle assembly of FIGS. **3-4**.

FIG. **6** is an enlarged vie of the needle assembly mounting means of the embodiment shown in FIGS. **3-5**.

FIG. **7** is a cut through view of the needle mount and needle hub illustrating one embodiment of the present invention for tacitly determining whether the needle hub is securely mounted on the needle mount.

FIG. **8** is a side view of a magazine for storing needles that may be used in practicing the method steps of the present invention.

FIG. **9** is a top view of the magazine shown in FIG. **8**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for systems and methods for attaching needle hub assemblies to ampoules and injection devices. Typically, a needle hub assembly comprises a needle **510** mounted to a hub **500** (see e.g. FIG. **3**). As is shown in FIG. **1**, a needle hub **10** may be generally cylindrically shaped and have an interior wall surface **20**. In one embodiment of the present invention, a plurality of protrusions **30** extends radially inward from the interior surface **20**.

A needle mount **100** is designed to accept the needle hub **10**. (See e.g. FIG. **1**). As is shown in FIGS. **1** and **2**, the needle mount **100** may be generally cylindrically shaped and have an exterior wall surface **110**. A plurality of grooves or slots **120** are disposed in the exterior surface **110**. The grooves **120** have a first end **122** and a second end **125**. The grooves **120** have a first portion **130** that defines a passageway that is generally parallel to the cylindrical axis **1000** of the needle mount **100**. While the first portion of the groove **130** is shown in the drawings as having a rectangular portion, the exact shape of the groove is not critical so long as it allows the protrusions **30** on the needle hub to move in a direction parallel to the cylindrical axis **1000**. Thus, while the groove may have walls that are not necessarily parallel to the cylindrical axis **1000**, the groove may still be said to be parallel to the cylindrical axis if it allows the protrusions **30** to move in a direction parallel to the cylindrical axis. The first portion of the grooves **130** may have width that is wider than the remainder of the first portion or the remainder of the groove **130**. In embodiments where the groove has walls that are not parallel to the cylindrical axis **1000**, the width of the first portion of the groove **130** may be the average width for the first portion of the groove **130**.

The first portion **130** may have an entrance **135** that has a width dimension that is greater than the average width of the first portion or is wider than the average width of the entire groove **120**. The entrance **135** may act as an alignment means for aligning the needle hub so that the protrusions will enter the groove **120**. In most embodiments, but not all, the entrance width is wider than any other point in the groove **120**. Typically the width of the groove narrows as the groove is traversed away from the entrance **135**. As is shown, the groove may reach a constant width at some distance from the opening. In some embodiments the width of the first portion **130** is widest at the entrance **135** and continues to narrow over the length of the first portion **130**. The grooves also have a second portion **150** that is either perpendicular to the cylindrical axis **1000**, or lies at angle to the first portion **130**. In some embodiments of the present invention the second portion **150** may be comprised of only one surface that is generally perpendicular to the cylindrical axis of the needle mount. Thus, the second portion of the groove **150** need not be a slot having two sides, but needs only one side to prevent protrusions on the needle hub from moving toward the outer end of the needle mount. As shown in FIG. **1**, the grooves **120** may also have a third portion **160** that is oriented at an angle to the first portion **130** and the second portion **150**.

In some embodiments of the present invention a means for tacitly determining whether the needle assembly is securely fixed to the hub is provided. This may be accomplished in numerous different ways, including providing a small projection(s) **439** at the side or in the bottom of the second portion of the grooves **120**. (See e.g. FIG. **7**). The protrusions **30** have to overcome the projections **439** before the needle is fixed. The deformation of the projections may cause a tacitly feel or a sound, such as a clicking sound. Thus, in some embodiments of the present invention, the needle mounting system can be designed so that the needle hub and the needle mount generate a clicking sound when the needle is securely placed on the mount. When the hub is to be remounted from injection device the oblique tactile protrusions can be more sharp at their ends, so that hub is better fixed during injection and handling etc. This also makes it possible for the patient to keep the needle for more injection.

One advantage of the present invention is that the needle mount, may be equipped with standard threads **200** on its exterior surface. (See FIG. **1**). The grooves **120** may be cut into the standard threads **200**. This allows the needle mount **100** to accept not only needle hubs of the present invention, but also standard, threaded needle-hub assemblies.

While FIG. **1** shows the grooves on the needle mount and the protrusions on the needle hub, the present invention may be configured with the grooves located on the interior surface of the needle hub and the protrusions extending outward from the exterior wall of the needle mount. In some, embodiments it may be advantageous to size and shape the protrusions so that they fit between standard threads used with existing needle hubs. The protrusions may then be arranged on the exterior wall of the needle mount to allow not only needle hub assemblies having grooves in their interior wall to be attached, but also standard, threaded needle hubs.

The present invention may take numerous other forms, including—but not limited to—that shown in FIGS. **3-6**. As is shown in FIGS. **3-6**. the needle hub assembly **500** has a needle **510** mounted thereto. The needle hub **550** may be generally cylindrically shaped and has an interior wall surface **600** and a closed top end **610**. The closed top end **610** has an inside surface **620**. A cylindrical member **650** protrudes from the inside surface **620** and has an outer surface **660**. See FIG. **5**. Protrusions **670** extend radially outward from the outer surface **660**. The protrusions may take various forms and shapes, including the triangular prism shape shown in the drawings.

The needle hub assembly shown in FIGS. **3-5** may be used with a modified needle mount, **700**. As is shown in FIGS. **3-6**, the needle mount **700** may be generally cylindrically shaped and have a top end, an interior surface, an exterior surface, and a plurality of locking elements (which may be additional protrusions) extending from the interior surface inward. The locking elements may be arranged to form passageways for the protrusions **500** on the needle mount, thereby forming a plurality of grooves for accepting the protrusions from the needle hub assembly **500**. As is shown in FIG. **6**, the grooves may have a first portion **561** that defines a passageway that is generally parallel to the cylindrical axis of the needle mount, a second portion **571** that is perpendicular to the cylindrical axis and a third portion **588** that connects the second **571** and first portions **561**. The first portion **561** may be widest at its opening and thus act as an alignment mechanism for the protrusions on the needle hub. The needle mount may have a mounting surface **581** on which a portion of the needle hub rests when the needle hub is mounted on the needle mount. The mounting surface may be a top edge of the top end of needle mount, or it may be the exterior wall surface **599** of the needle mount or both. The embodiment shown in FIGS. **2-4** also advantageously allows the outer surface of the needle mount to have threads so that standard prior-art needle hubs may be used with the improved needle mount of the present invention.

The present invention enables various methods for attaching a needle-hub assembly to an ampoule or injection device. For example, in one embodiment of the present invention, a needle mount is inserted into a needle hub, the needle hub is rotate relative to the needle mount less than one revolution—typically between 5 and 30 to 60 degrees. In some embodiments, a clicking noise or vibration or other tactile feedback will be provided to indicate that the needle is securely mounted to the hub. In some embodiments little rotation is necessary. In some embodiments, it is possible that no rotation is needed. The surface of the locking element **777** could simply force the hub to rotate upon insertion of the mount into the interior of the hub **500**. In other embodiments, more rotation may be required.

Because the methods of mounting a needle hub to a needle mount do not require that the hub be rotated a full revolution relative to the mount (i.e. either the hub is rotated and the mount is held stationary or the mount is rotated and the hub is held stationary, or both are turned in opposite direction), the present invention enables and provides for methods of mounting needle-hub assemblies stored in magazines, similar to that shown in FIGS. **8** and **9**, to injection devices where their shape would not allow the device to be rotated relative to the magazine by a full revolution. In one embodiment of the present invention, a portion of an injection device **3000**, usually the portion containing a needle mount **3010**, is inserted into a needle magazine **3050**. The device **3000**, without being rotated a full revolution is then removed with a needle fully attached to it. In some embodiments audible or tactile feedback is provided to indicate that the need is securely mounted to the device. In some embodiments, the portion of the device that is inserted into the magazine may be an end portion of an ampoule that extends from the device. Some methods of practicing the present invention may be performed using the needles are stored in a magazine having a flush surface **3070** and the needle and hub assemblies **3080** are located below the surface **3070**, usually—but not necessarily—in recessed cavities **3090** (see FIG. **9**).

The foregoing is a brief description of some exemplary embodiments of the present invention and is intended to be illustrative and not exhaustive of the present invention. Those of skill in the art will recognize the nature of language makes it impossible to capture the essence of all aspects of the present invention and unimportant and insubstantial substitutes for various elements are intended to be included within the scope of the invention as defined by the following claims.

The invention claimed is:

1. A needle mount comprising two separate coupling mechanisms comprising a first coupling mechanism and a second coupling mechanism, the needle mount comprising:

a cylindrical outer wall having a top end and threads disposed on the cylindrical outer wall,

the first coupling mechanism comprising a plurality of grooves disposed in a cylindrical outer wall beginning at the top end of the cylindrical outer wall and defining a passageway that is generally parallel to a cylindrical axis of the cylindrical outer wall, and wherein at least one groove of the needle mount comprises a first portion and a second portion oriented at an angle to the first portion, wherein the first portion and second portion do not form a part of the second coupling mechanism, and wherein at least one protrusion(s) of a needle hub, when present, interact with at least one groove(s) to form a bayonet coupling,

the second coupling mechanism comprising threads disposed on the cylindrical outer wall, suitable for threadedly connecting and matingly fitting a conventional threaded needle assembly to the needle mount,

the needle mount thereby allowing either a threaded needle hub to be mounted or dismounted onto the needle mount via a second coupling mechanism, or a bayonet needle hub to be mounted or dismounted onto the needle mount via the first coupling mechanism.

2. The needle mount according to claim **1**, wherein the angle between the first portion and the second portion is 90 degrees or less.

3. The needle mount according to claim 1, wherein the first portion of the groove is widest at the top end of the needle mount defining an entrance.

4. The needle mount according to claim 1, wherein the protrusions of the needle hub, when present, comprise a circular surface.

5. The needle mount according to claim 1, further comprising structure for determining whether the needle hub is securely mounted on the needle mount.

6. The needle mount according to claim 1, wherein the needle mount is on an adapter top that is secured to an ampoule, or an injection device.

* * * * *

EXHIBIT B

US007762994B2

(12) **United States Patent**
Klint et al.

(10) **Patent No.: US 7,762,994 B2**
(45) **Date of Patent: Jul. 27, 2010**

(54) **NEEDLE MOUNTING SYSTEM AND A METHOD FOR MOUNTING A NEEDLE ASSEMBLY**

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(21) Appl. No.: **11/778,274**

(22) Filed: **Jul. 16, 2007**

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(60) Provisional application No. 60/394,083, filed on Jul. 3, 2002.

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A61M 5/00 (2006.01)

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(58) **Field of Classification Search** 604/240, 604/241, 242, 243, 93.01, 181, 187, 188, 604/272, 533–535, 538
See application file for complete search history.

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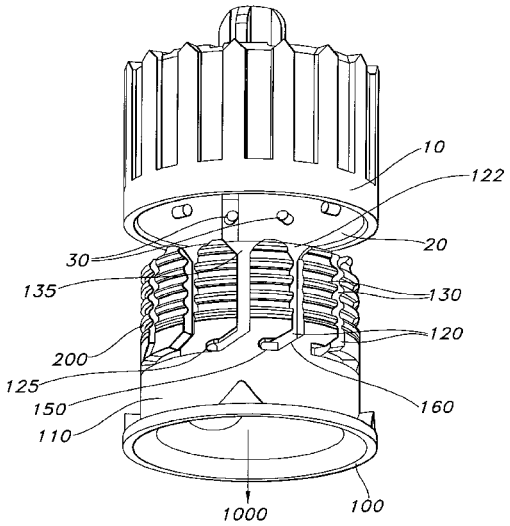
Primary Examiner—Kevin C Sirmons
Assistant Examiner—Laura C Schell
(74) *Attorney, Agent, or Firm*—Wesley A. Nicolas; Marc A. Began; Reza Green

(57) **ABSTRACT**

A needle mounting system and methods for mounting a needle assembly on a needle mount are disclosed. The needle mounting system includes a needle hub having protrusions extending radially inward. A needle mount has a plurality of slots to receive the protrusions. The slots have a first portion that defines a passageway substantially parallel to a longitudinal axis of the needle mount and a second portion substantially perpendicular to the axis. The needle hub and mount provide a method wherein a needle assembly may be mounted on an injection device without completely rotating the needle hub relative to the needle mount.

8 Claims, 8 Drawing Sheets



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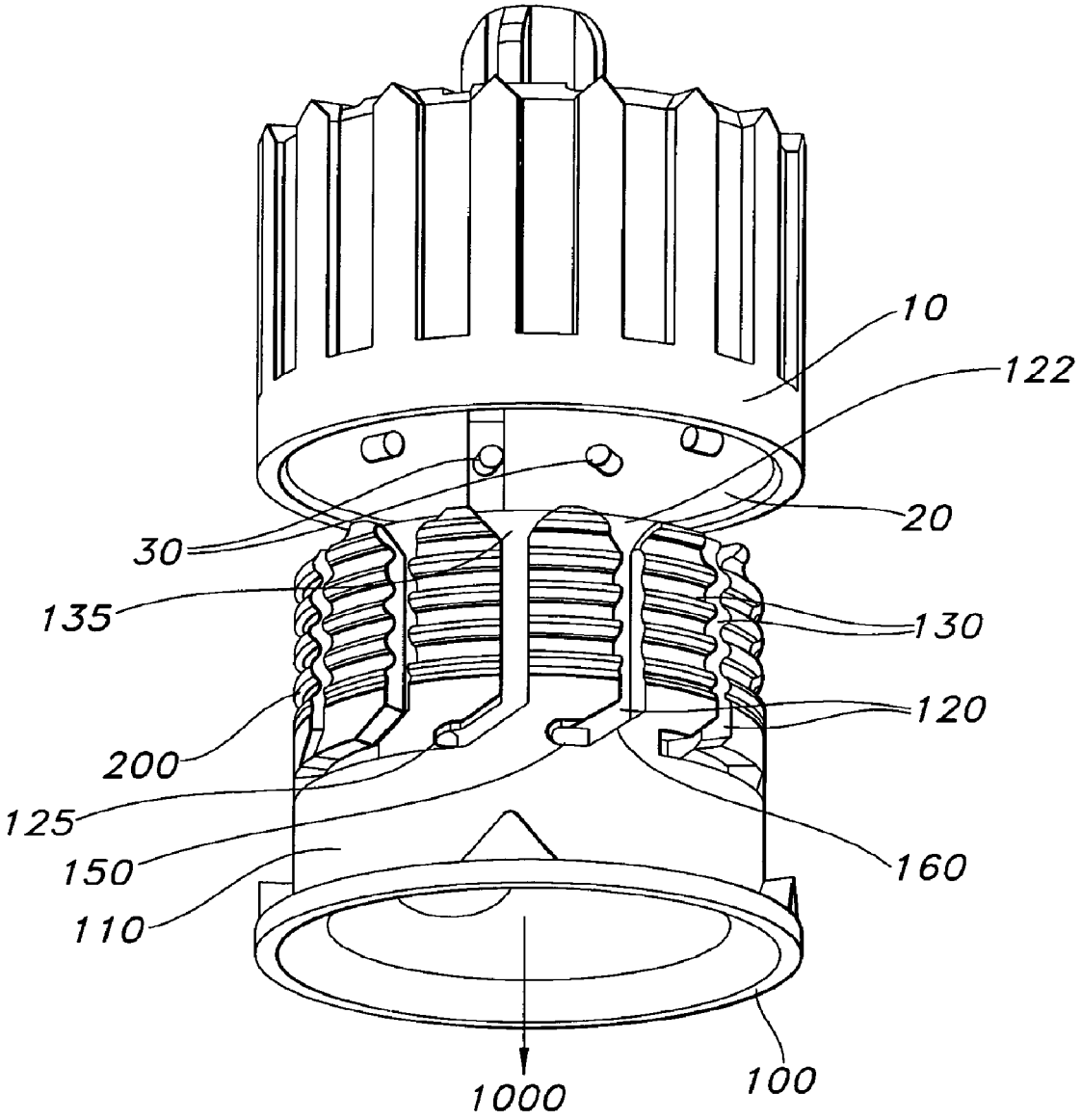

FIG. 1

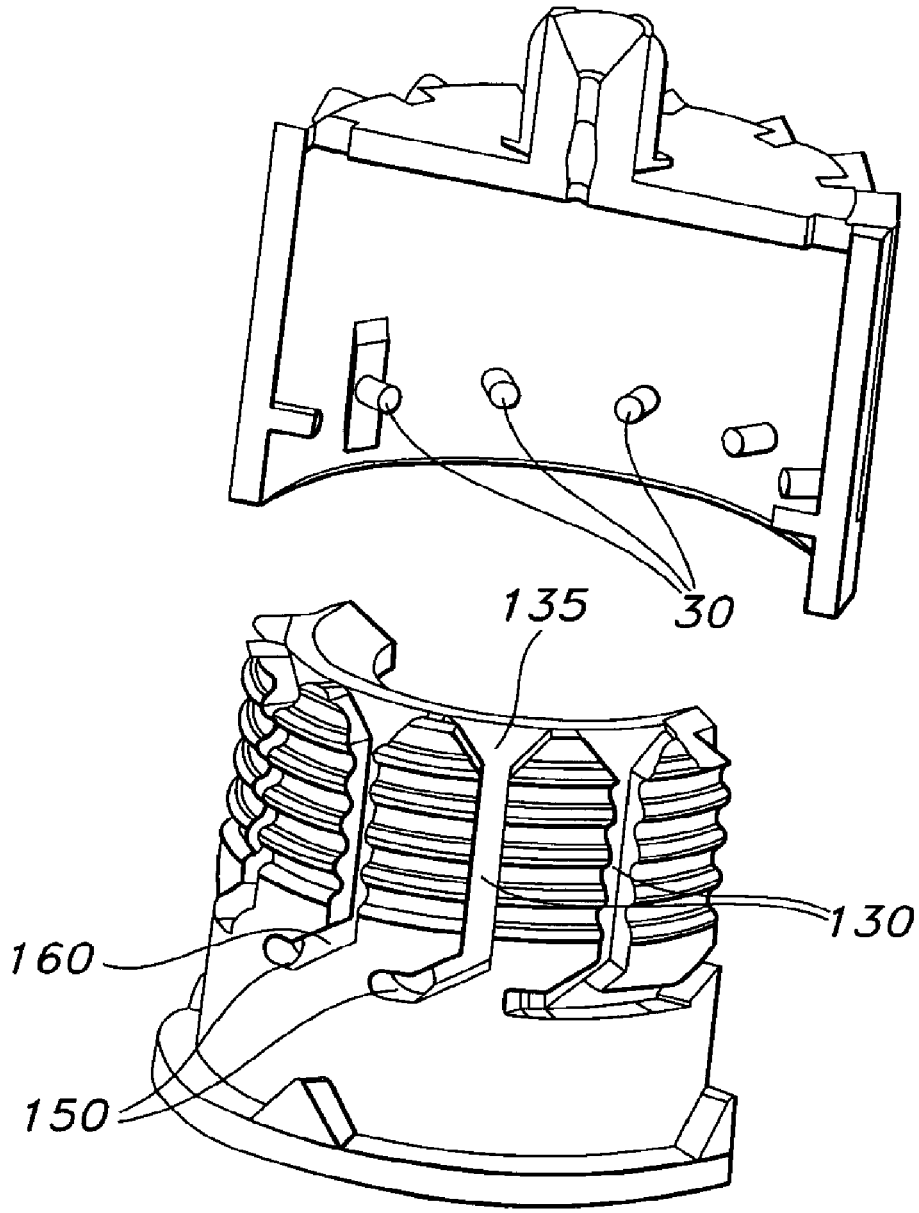

FIG. 2

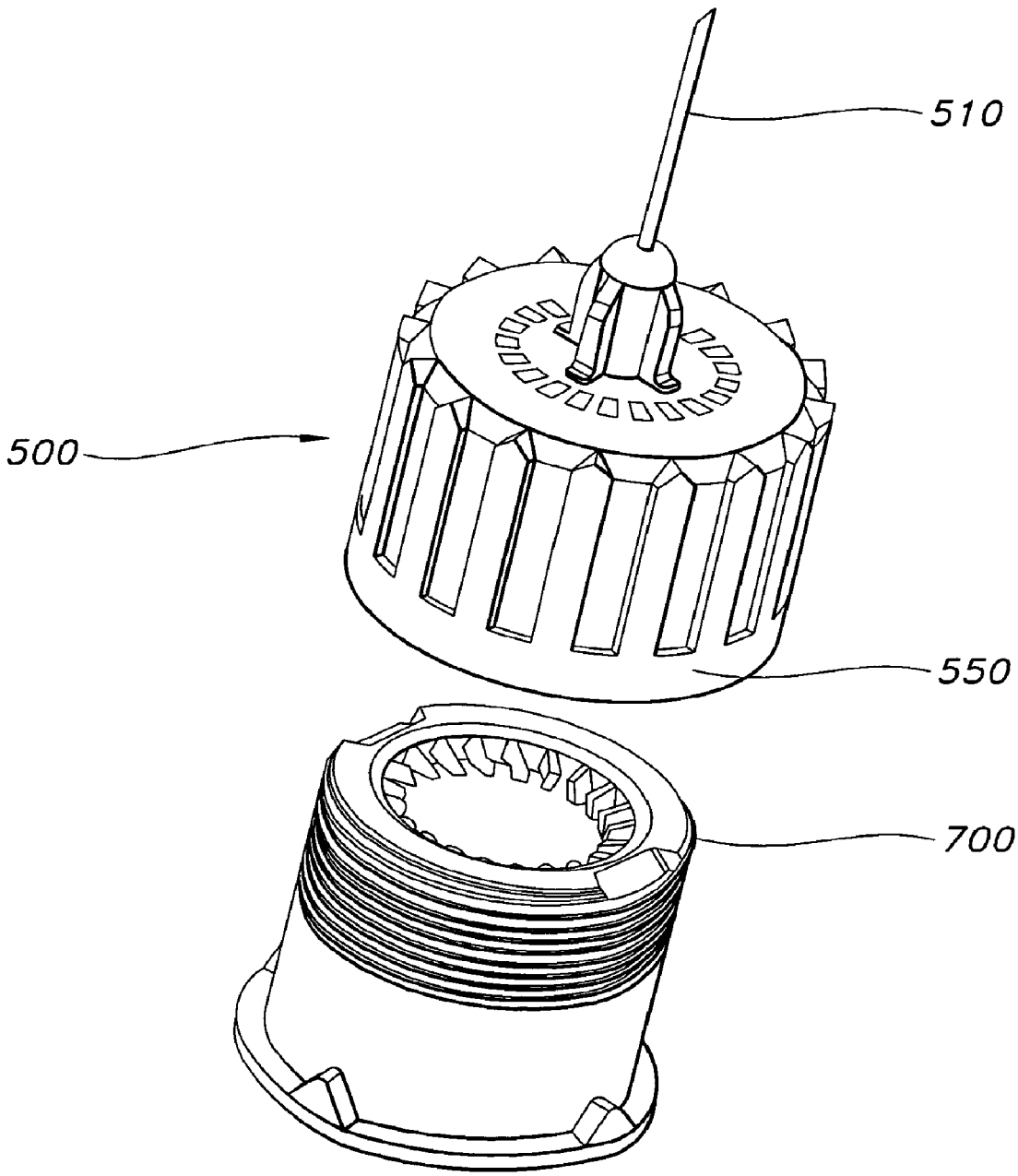

FIG. 3

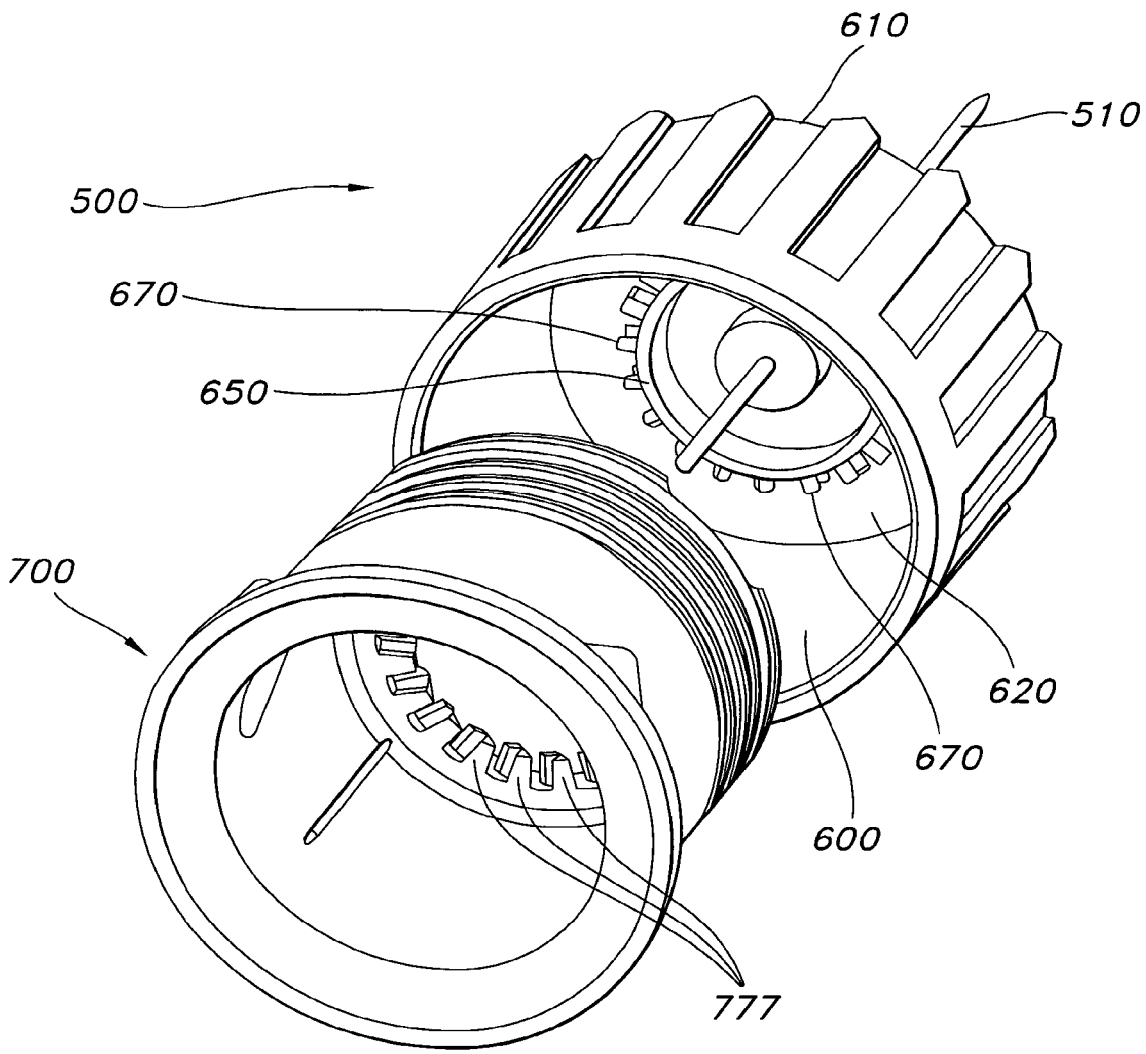

FIG. 4

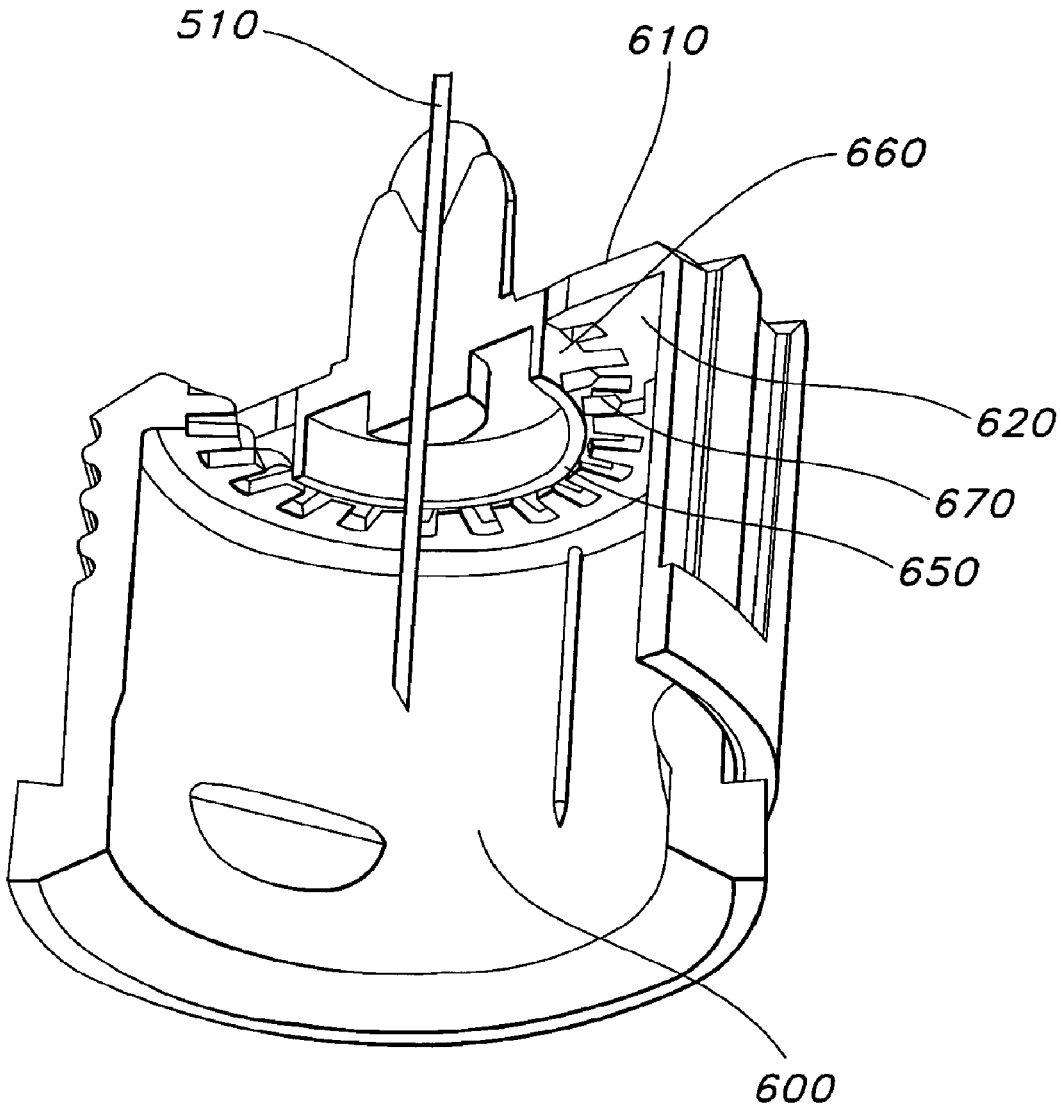

FIG. 5

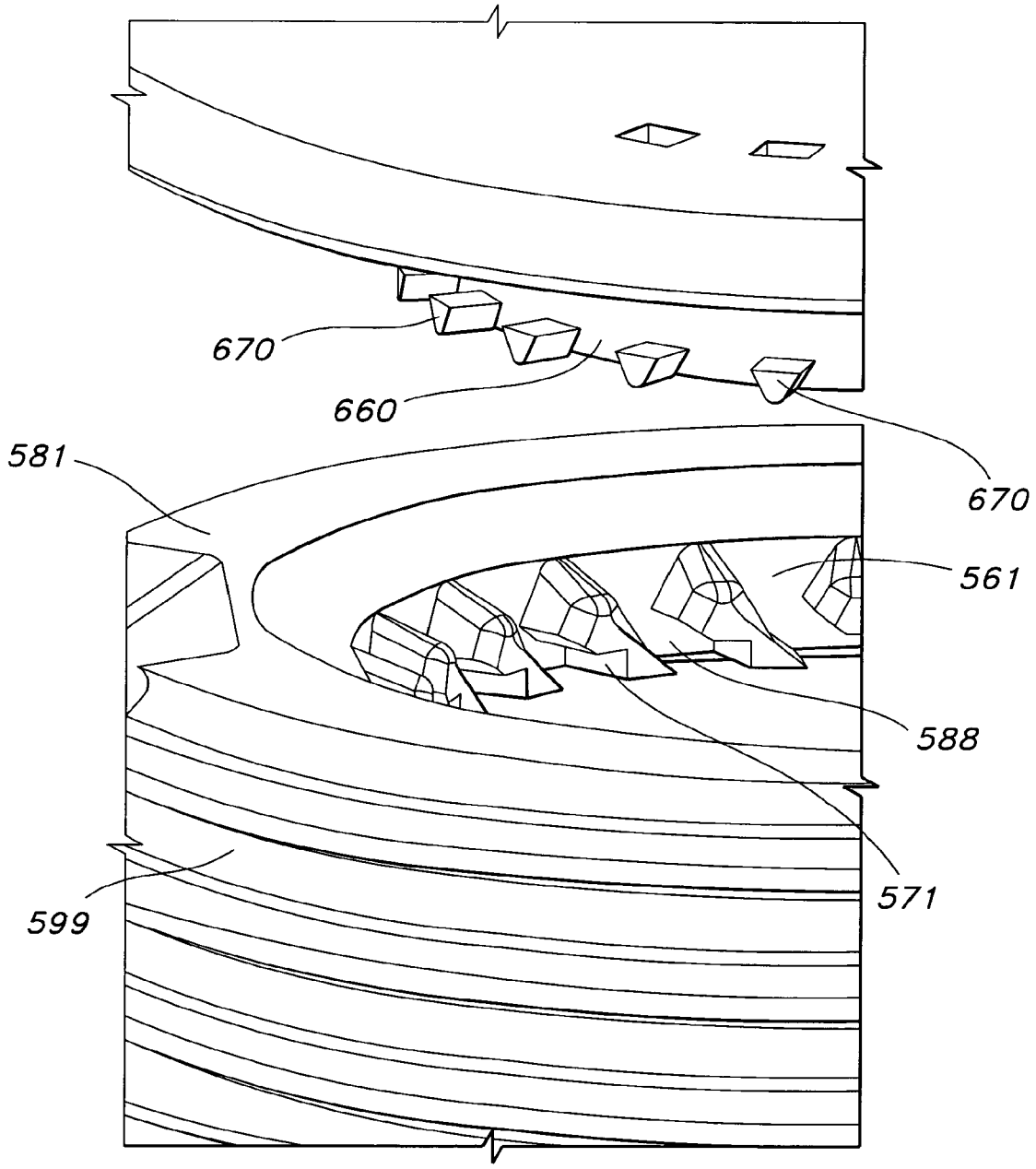

FIG. 6

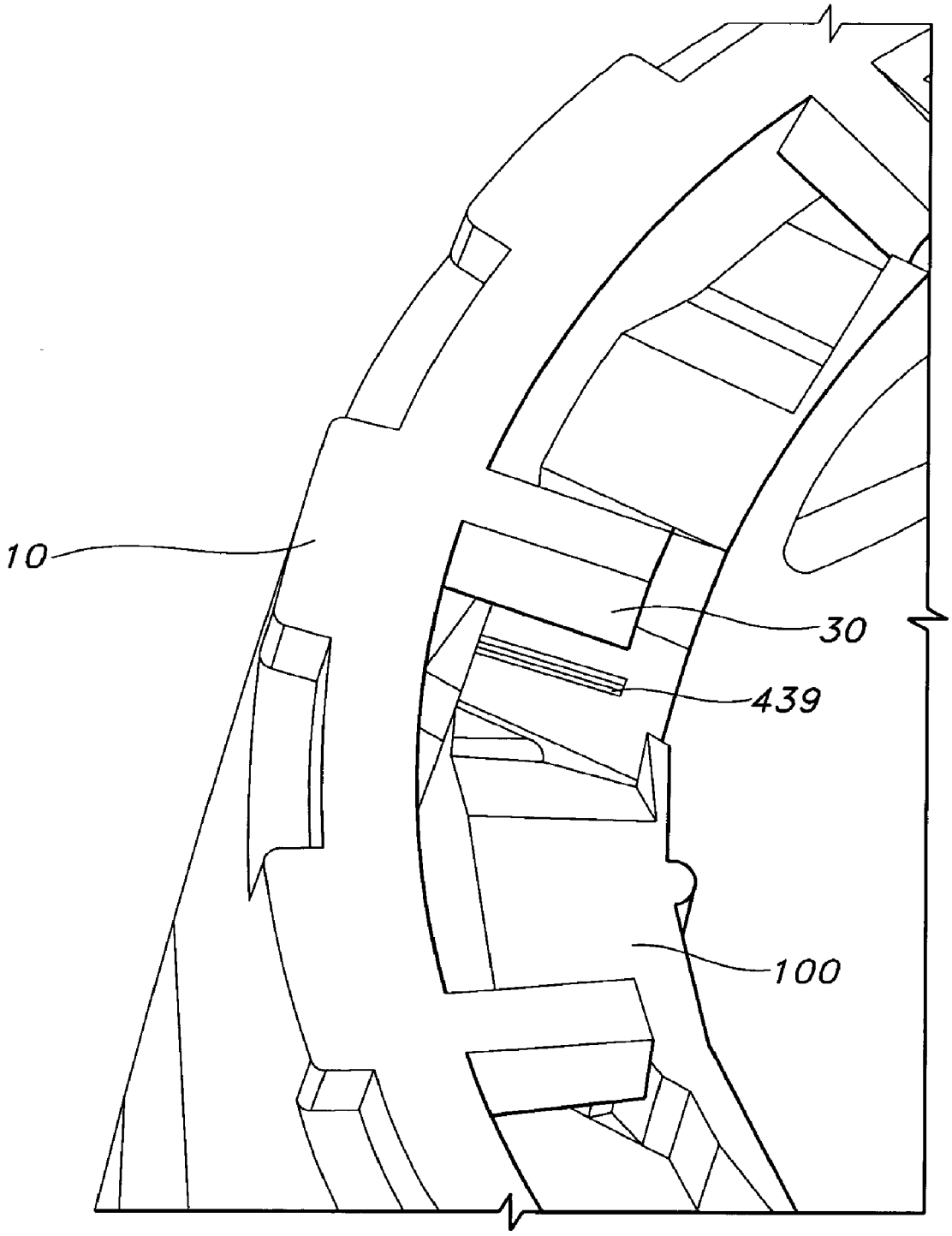

FIG. 7

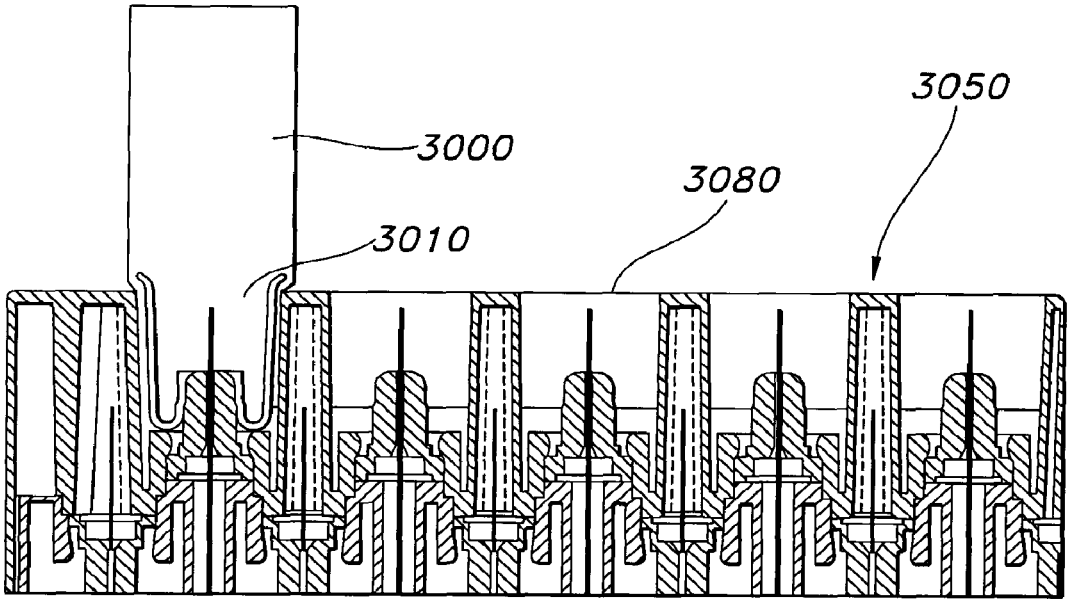

FIG. 8

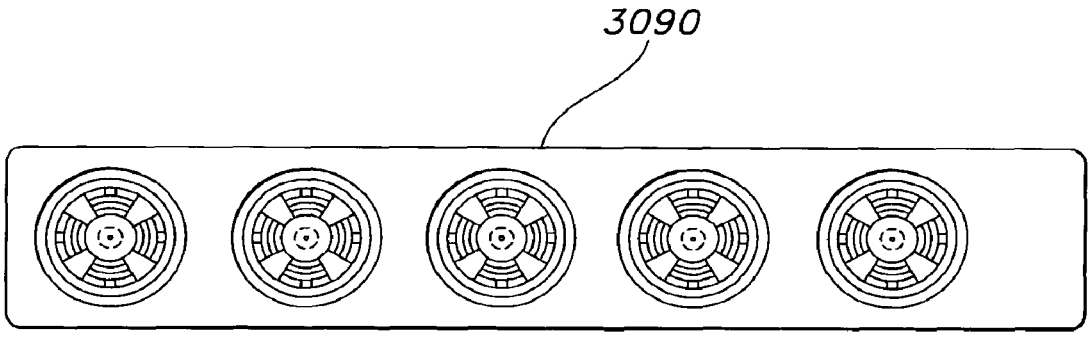

FIG. 9

NEEDLE MOUNTING SYSTEM AND A METHOD FOR MOUNTING A NEEDLE ASSEMBLY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of application Ser. No. 10/609,744 filed on Jun. 30, 2003, now U.S. Pat. No. 7,654,986, which claims priority under 35 U.S.C. 119 of Danish application no. PA 2002 01169 filed Aug. 1, 2002, and U.S. provisional application No. 60/394,083 filed Jul. 3, 2002, the contents of which are fully incorporated herein by reference.

THE TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to injection devices and, in particular, provides methods and systems for mounting a needle to an injection device or to an ampoule that my be mounted in the injection device.

DESCRIPTION OF RELATED ART

Injection devices, also referred to as dosers, have greatly improved the lives of patients who must self-adminster drugs and biological agents. Dosers may take many forms, including simple disposable devices that are little more than an ampoule with an injection means or they may be highly sophisticated instruments with numerous functions. Regardless of their form, they have proven to be great aids in assisting patients to self-adminster injectable drugs and biological agents. They also greatly assist care givers in administering injectable medicines to those incapable of performing self-injections.

In particular, pen-style injection devices, have proven to be an accurate, convenient, and often discrete, way to administer drugs and biological agents, such as insulin. Modern devices have become more sophisticated and often include diverse and robust functions, such as memories for remembering time and amount of last dose, as well as, in the case of insulin devices, blood glucose monitors. While pen-style dosers are typically cylindrically shaped with needles protruding from the most distal portion of one end of the device, some of the more modern and/or sophisticated dosers have other shapes with the needle no longer protruding from the most distal part of an end of the device. (See e.g., Innovo® and InnoLet® from Novo Nordisk A/S Bagsvaerd Denmark).

Typically, injection devices use a pre-filled cartridge containing the medication of interest. The cartridge may be an integral part of the doser or it may comprise an ampoule having a membrane at one. See U.S. Pat. No. 6,312,413 to Jensen et. al, which is hereby incorporated by reference. Often the end of the ampoule having the membrane is fitted with a needle mount. The needle mount usually comprises a threaded mounting surface to allow a needle assembly, such as a needle and hub assembly, to be screwed on. The needle mount may be an integral part of the ampoule or may be a separate adapter top (see U.S. Pat. Nos. 5,693,027 and 6,126,646, which are hereby incorporated by reference) that is mounted to the ampoule. Of course, some dosers have needle mounts that are integral parts of the doser.

In the typical injection device where the needle mount is not part of the doser, the end of the ampoule having the needle mount protrudes from the injection device. Where the needle mount is part of the doser, the needle mount is usually disposed on an outer end of the doser. In either embodiment, the needle hub is then screwed onto the needle mount. One disadvantage of the prior art needle mounting systems is that they require the patient to screw the needle hub onto the end of the ampoule, or the doser, by turning the needle relative to the device several times. For patients with dexterity problems, this is inconvenient. Moreover, it is often desirable to store needles for the injection devices in a magazine. Often many newer generation injection devices are not cylindrical and in many new devices, other parts of the device extend past the needle mount making it impossible to mount the needle on the injection device without first removing it from the magazine.

SUMMARY OF THE INVENTION

The present invention provides systems and methods for mounting needle assemblies to injection devices and/or ampoules. In some, but not necessarily all embodiments, the system and method of the present invention allows a needle and hub assembly to be mounted on an ampoule and/or injection device without having to rotate completely the needle hub assembly relative to the injection device. In one embodiment of the present invention, a needle assembly is comprised of a needle mounted in a hub. The needle assembly also includes a means for mounting the hub to a needle mount with only a partial rotation of the needle hub relative to the mount. In an other embodiment of the present invention, a needle mount for mounting the needle assembly is comprised of an outer wall and a mounting means for affixing the needle assembly to a top end of the outer wall. In some embodiments, the means provides for completely securing the needle assembly to the needle mount with only a partial rotation of the needle mount. In some embodiments, the needle mount includes a means for aligning the needle assembly on the mounting means. The needle mount and needle assemblies of the present invention, when combined, make up a needle mounting system. The system, or its components, may also include a means for tactilely or audibly determining when the needle assembly is securely mounted on the needle mount.

At least one embodiment of the present invention includes a needle assembly that is comprised of a needle mounted to a hub having an interior wall. In this embodiment, a plurality of protrusions extends radially inward from the wall of the hub. Typically, the hub wall is cylindrical. A needle mount for use with the present invention, may in at least one embodiment, include a structure having a cylindrical outer wall. A plurality of grooves is disposed on the outer wall. The grooves begin at the top of the wall and contain at least two portions: a first portion that defines a passageway that is substantially parallel to the cylindrical axis of the outer wall, and a second portion that is oriented at an angle to the first portion. Of course, the present invention may be embodied in structures wherein the grooves are disposed inside the hub of the needle mount and the protrusions are disposed on an outer surface of the needle mount.

In at least one embodiment of the present invention, the needle assembly is completely mounted on an injection device with only a partial rotation of the needle assembly relative to the injection device. (Those skilled in the art will recognize that rotation of the needle assembly relative to the injection device may be accomplished by holding the device stationary and rotating the needle assembly or by holding the needle assembly stationary and rotating the device or by a combination of these steps). In some embodiments, the needle is mounted on an ampoule that is mounted in the injection device.

The present invention therefore provides a method for mounting needles to injection devices. The method may be useful in mounting needles stored in magazines and is par-

ticularly useful for injection devices that have a portion that extends past the needle mount. In one embodiment, the injection device is partially inserted into a magazine holding needle assemblies. The injection device is rotated relative to the magazine by less than a full revolution and is then removed with the needle assembly attached thereto. In some embodiments no or minimal rotation is required.

In other embodiments of the present invention, the needle assembly may include a cylindrical hub that has a needle mounted thereon. The hub may have an internal cylindrical element with an outside cylindrical wall that faces the hub's inside cylindrical wall. A plurality of protrusions may extend radially outward from the internal cylindrical element. A corresponding needle mount may be used. The needle mount, in one embodiment, may include a plurality of locking elements arranged on an interior cylindrical surface (e.g., a wall) of the needle mount to form first passageways that are substantially parallel to the cylindrical axis of the needle hub. In some embodiments, the locking elements are disposed on a ring that is part of the interior surface or that is attached to, or part of, an inside wall of the needle mount.

Further the protrusions could be sized to fit between threads of a standard ampoule adapter top. The protrusions arranged on the inner hub wall and aligned between the threads of a standard adapter top would allow the needle assembly to be screwed onto the adapter top in a traditional manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a three-dimensional view of a needle hub and needle mount according to one embodiment of the present invention.

FIG. **2** is a cut-away view of the needle mount and needle hub shown in FIG. **1**.

FIG. **3** is a three-dimensional view of a needle assembly and needle mount according to a second embodiment of the present invention.

FIG. **4** illustrates the embodiment of FIG. **3** when viewed from below.

FIG. **5** is a cut-way view of the needle assembly of FIGS. **3-4**.

FIG. **6** is an enlarged view of the needle assembly mounting means of the embodiment shown in FIGS. **3-5**.

FIG. **7** is a cut through view of the needle mount and needle hub illustrating one embodiment of the present invention for tacitly determining whether the needle hub is securely mounted on the needle mount.

FIG. **8** is a side view of a magazine for storing needles that may be used in practicing the method steps of the present invention.

FIG. **9** is a top view of the magazine shown in FIG. **8**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for systems and methods for attaching needle hub assemblies to ampoules and injection devices. Typically, a needle hub assembly comprises a needle **510** mounted to a hub **500** (see e.g. FIG. **3**). As is shown in FIG. **1**, a needle hub **10** may be generally cylindrically shaped and have an interior wall surface **20**. In one embodiment of the present invention, a plurality of protrusions **30** extends radially inward from the interior surface **20**.

A needle mount **100** is designed to accept the needle hub **10**. (See e.g. FIG. **1**). As is shown in FIGS. **1** and **2**, the needle mount **100** may be generally cylindrically shaped and have an exterior wall surface **110**. A plurality of grooves or slots **120** are disposed in the exterior surface **110**. The grooves **120** have a first end **122** and a second end **125**. The grooves **120** have a first portion **130** that defines a passageway that is generally parallel to the cylindrical axis **1000** of the needle mount **100**. While the first portion of the groove **130** is shown in the drawings as having a rectangular portion, the exact shape of the groove is not critical so long as it allows the protrusions **30** on the needle hub to move in a direction parallel to the cylindrical axis **1000**. Thus, while the groove may have walls that are not necessarily parallel to the cylindrical axis **1000**, the groove may still be said to be parallel to the cylindrical axis if it allows the protrusions **30** to move in a direction parallel to the cylindrical axis. The first portion of the grooves **130** may have width that is wider than the remainder of the first portion or the remainder of the groove **130**. In embodiments where the groove has walls that are not parallel to the cylindrical axis **1000**, the width of the first portion of the groove **130** may be the average width for the first portion of the groove **130**.

The first portion **130** may have an entrance **135** that has a width dimension that is greater than the average width of the first portion or is wider than the average width of the entire groove **120**. The entrance **135** may act as an alignment means for aligning the needle hub so that the protrusions will enter the groove **120**. In most embodiments, but not all, the entrance width is wider than any other point in the groove **120**. Typically the width of the groove narrows as the groove is traversed away from the entrance **135**. As is shown, the groove may reach a constant width at some distance from the opening. In some embodiments the width of the first portion **130** is widest at the entrance **135** and continues to narrow over the length of the first portion **130**. The grooves also have a second portion **150** that is either perpendicular to the cylindrical axis **1000**, or lies at angle to the first portion **130**. In some embodiments of the present invention the second portion **150** may be comprised of only one surface that is generally perpendicular to the cylindrical axis of the needle mount. Thus, the second portion of the groove **150** need not be a slot having two sides, but needs only one side to prevent protrusions on the needle hub from moving toward the outer end of the needle mount. As shown in FIG. **1**, the grooves **120** may also have a third portion **160** that is oriented at an angle to the first portion **130** and the second portion **150**.

In some embodiments of the present invention a means for tacitly determining whether the needle assembly is securely fixed to the hub is provided. This may be accomplished in numerous different ways, including providing a small projection(s) **439** at the side or in the bottom of the second portion of the grooves **120**. (See e.g. FIG. **7**). The protrusions **30** have to overcome the projections **439** before the needle is fixed. The deformation of the projections may cause a tacitly feel or a sound, such as a clicking sound. Thus, in some embodiments of the present invention, the needle mounting system can be designed so that the needle hub and the needle mount generate a clicking sound when the needle is securely placed on the mount. When the hub is to be remounted from injection device the oblique tactile protrusions can be more sharp at their ends, so that hub is better fixed during injection and handling etc. This also makes it possible for the patient to keep the needle for more injection.

One advantage of the present invention is that the needle mount, may be equipped with standard threads **200** on its exterior surface. (See FIG. **1**). The grooves **120** may be cut into the standard threads **200**. This allows the needle mount **100** to accept not only needle hubs of the present invention, but also standard, threaded needle-hub assemblies.

While FIG. **1** shows the grooves on the needle mount and the protrusions on the needle hub, the present invention may be configured with the grooves located on the interior surface of the needle hub and the protrusions extending outward from the exterior wall of the needle mount. In some, embodiments it may be advantageous to size and shape the protrusions so that they fit between standard threads used with existing needle hubs. The protrusions may then be arranged on the exterior wall of the needle mount to allow not only needle hub assemblies having grooves in their interior wall to be attached, but also standard, threaded needle hubs.

The present invention may take numerous other forms, including—but not limited to—that shown in FIGS. **3-6**. As is shown in FIGS. **3-6**. the needle hub assembly **500** has a needle **510** mounted thereto. The needle hub **550** may be generally cylindrically shaped and has an interior wall surface **600** and a closed top end **610**. The closed top end **610** has an inside surface **620**. A cylindrical member **650** protrudes from the inside surface **620** and has an outer surface **660**. See FIG. **5**. Protrusions **670** extend radially outward from the outer surface **660**. The protrusions may take various forms and shapes, including the triangular prism shape shown in the drawings.

The needle hub assembly shown in FIGS. **3-5** may be used with a modified needle mount, **700**. As is shown in FIGS. **3-6**, the needle mount **700** may be generally cylindrically shaped and have a top end, an interior surface, an exterior surface, and a plurality of locking elements (which may be additional protrusions) extending from the interior surface inward. The locking elements may be arranged to form passageways for the protrusions **500** on the needle mount, thereby forming a plurality of grooves for accepting the protrusions from the needle hub assembly **500**. As is shown in FIG. **6**, the grooves may have a first portion **561** that defines a passageway that is generally parallel to the cylindrical axis of the needle mount, a second portion **571** that is perpendicular to the cylindrical axis and a third portion **588** that connects the second **571** and first portions **561**. The first portion **561** may be widest at its opening and thus act as an alignment mechanism for the protrusions on the needle hub. The needle mount may have a mounting surface **581** on which a portion of the needle hub rests when the needle hub is mounted on the needle mount. The mounting surface may be a top edge of the top end of needle mount, or it may be the exterior wall surface **599** of the needle mount or both. The embodiment shown in FIGS. **2-4** also advantageously allows the outer surface of the needle mount to have threads so that standard prior-art needle hubs may be used with the improved needle mount of the present invention.

The present invention enables various methods for attaching a needle-hub assembly to an ampoule or injection device. For example, in one embodiment of the present invention, a needle mount is inserted into a needle hub, the needle hub is rotate relative to the needle mount less than one revolution—typically between 5 and 30 to 60 degrees. In some embodiments, a clicking noise or vibration or other tactile feedback will be provided to indicate that the needle is securely mounted to the hub. In some embodiments little rotation is necessary. In some embodiments, it is possible that no rotation is needed. The surface of the locking element **777** could simply force the hub to rotate upon insertion of the mount into the interior of the hub **500**. In other embodiments, more rotation may be required.

Because the methods of mounting a needle hub to a needle mount do not require that the hub be rotated a full revolution relative to the mount (i.e. either the hub is rotated and the mount is held stationary or the mount is rotated and the hub is held stationary, or both are turned in opposite direction), the present invention enables and provides for methods of mounting needle-hub assemblies stored in magazines, similar to that shown in FIGS. **8** and **9**, to injection devices where their shape would not allow the device to be rotated relative to the magazine by a full revolution. In one embodiment of the present invention, a portion of an injection device **3000**, usually the portion containing a needle mount **3010**, is inserted into a needle magazine **3050**. The device **3000**, without being rotated a full revolution is then removed with a needle fully attached to it. In some embodiments audible or tactile feedback is provided to indicate that the need is securely mounted to the device. In some embodiments, the portion of the device that is inserted into the magazine may be an end portion of an ampoule that extends from the device. Some methods of practicing the present invention may be performed using the needles are stored in a magazine having a flush surface **3070** and the needle and hub assemblies **3080** are located below the surface **3070**, usually—but not necessarily—in recessed cavities **3090** (see FIG. **9**).

The foregoing is a brief description of some exemplary embodiments of the present invention and is intended to be illustrative and not exhaustive of the present invention. Those of skill in the art will recognize the nature of language makes it impossible to capture the essence of all aspects of the present invention and unimportant and insubstantial substitutes for various elements are intended to be included within the scope of the invention as defined by the following claims.

What is claimed:

1. A mounting system for mounting two different needle arrangements, the mounting system comprising:

a generally cylindrical shaped body having a distal end;

a first coupling mechanism and a second coupling mechanism, wherein the first coupling mechanism and the second coupling mechanism are separate and at the same end segment,

the first coupling mechanism comprising a plurality of grooves disposed in a cylindrical outer wall on the generally cylindrically shaped body and defining a passageway that is generally parallel to a cylindrical axis of the generally cylindrical body, and wherein at least one groove of the first coupling mechanism comprises a first portion and a second portion oriented at an angle to the first portion, wherein the first portion and second portion do not form a part of the second coupling mechanism and wherein protrusions of a needle hub when present interact with the grooves to form a bayonet coupling, and

the second coupling mechanism comprising male threads disposed on the distal end suitable for threadedly connecting and matingly fitting a threaded needle assembly to the needle mount,

thereby allowing either a threaded needle hub to be mounted or dismounted onto the needle mount via the second coupling mechanism, or a bayonet needle hub to be mounted or dismounted onto the needle mount via the first coupling mechanism.

2. The mounting system according to claim **1**, wherein the angle between the first portion and the second portion is 90 degrees or less.

3. The mounting system according to claim **1**, wherein the first portion being widest at the top end forms an entrance.

4. The needle mount according to claim **1**, wherein the first portion and the second portion form a substantially L-shaped groove.

5. A mounting system for mounting two different needle arrangements on a generally cylindrically shaped injection device that contains a cartridge from which medication is to be injected into a subject,

wherein a first type of double point needle arrangement comprises a double point hollow needle located within a

tubular member having a cylindrical inner wall containing one or more protrusions that extends radially inward from the inner wall, and

a second type of needle arrangement comprises a second hollow needle fixed in a conventional pen needle hub, the hub being generally cylindrical and having an interior adapted for being screwed on or off of a male threaded needle mounting surface on the injection device, the needle mount system comprising:

a first coupling mechanism and a second coupling mechanism, wherein the first coupling mechanism and the second coupling mechanism are at the same end segment,

the first coupling mechanism comprising a bayonet coupling which comprises a plurality of grooves disposed on an outer cylindrical surface of the injection device, the grooves having a first longitudinal portion extending in substantially parallel to a longitudinal axis of the injection device and having a second portion that extends at an angle from the first portion;

the second coupling mechanism being generally cylindrical in shape and comprising an external male thread for creating a screwed arrangement between the conventional pen needle hub and the injection device which thereby allows the conventional pen needle to be screwed on or off of the injection device;

whereby the needle mount system allows a first needle arrangement to be secured to the injection device via the first coupling mechanism and allows the needle to be removed by less than a full rotation of the bayonet coupling and whereby a second needle arrangement can be mounted on the second coupling mechanism and be removed by threadedly unscrewing the needle from the device.

6. The mounting system of claim **5**, wherein the first needle arrangement may be removed from the device by rotating the tubular member less than one revolution.

7. The mounting system of claim **6**, wherein the second needle is removed by rotating the second needle multiple revolutions.

8. A mounting system for mounting two different needle arrangements onto the same end segment of an injection device that contains a container from which medication is to be injected into a patient; the system comprising two independent coupling mechanisms for securing the different needle arrangements to the device,

the first coupling comprising longitudinal groove in an outer cylindrical wall of the device wherein the grooves comprise a first portion substantially parallel to a longitudinal axis of the device and further comprise a second portion oriented at an angle to the first portion, wherein the first coupling is adapted for mounting a cylindrical member surrounding a hollow needle to the device, wherein the cylindrical member comprises an inner wall having protrusions that extend radially inward and engage the first portion of the groove as the cylinder is displaced axially and then engage the second portion of the groove as the cylinder is rotated;

the second coupling comprising a male thread located at the distal end of the injection device that engages an inner wall of a cylindrical pen needle hub, wherein the engagement allows the needle hub to be screwed onto or off of the male thread;

thereby allowing a first needle to be placed on the injection device and to be removed by less than a full rotation of device relative to the first needle arrangement and allows a second needle then be secured to the device via an engagement between the pen needle hub and the male thread.

* * * * *

EXHIBIT C

US008114833B2

(12) **United States Patent**
Pedersen et al.

(10) **Patent No.: US 8,114,833 B2**
(45) **Date of Patent: *Feb. 14, 2012**

(54) **PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 663 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/435,977**

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(65) **Prior Publication Data**

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(63) Continuation of application No. PCT/DK2004/000792, filed on Nov. 18, 2004.

(60) Provisional application No. 60/524,653, filed on Nov. 24, 2003.

(30) **Foreign Application Priority Data**

Nov. 20, 2003 (DK) 2003 01719

(51) **Int. Cl.**
A61K 38/26 (2006.01)

(52) **U.S. Cl.** **514/2**; 530/308

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

31 Claims, 7 Drawing Sheets

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FIGURE 1

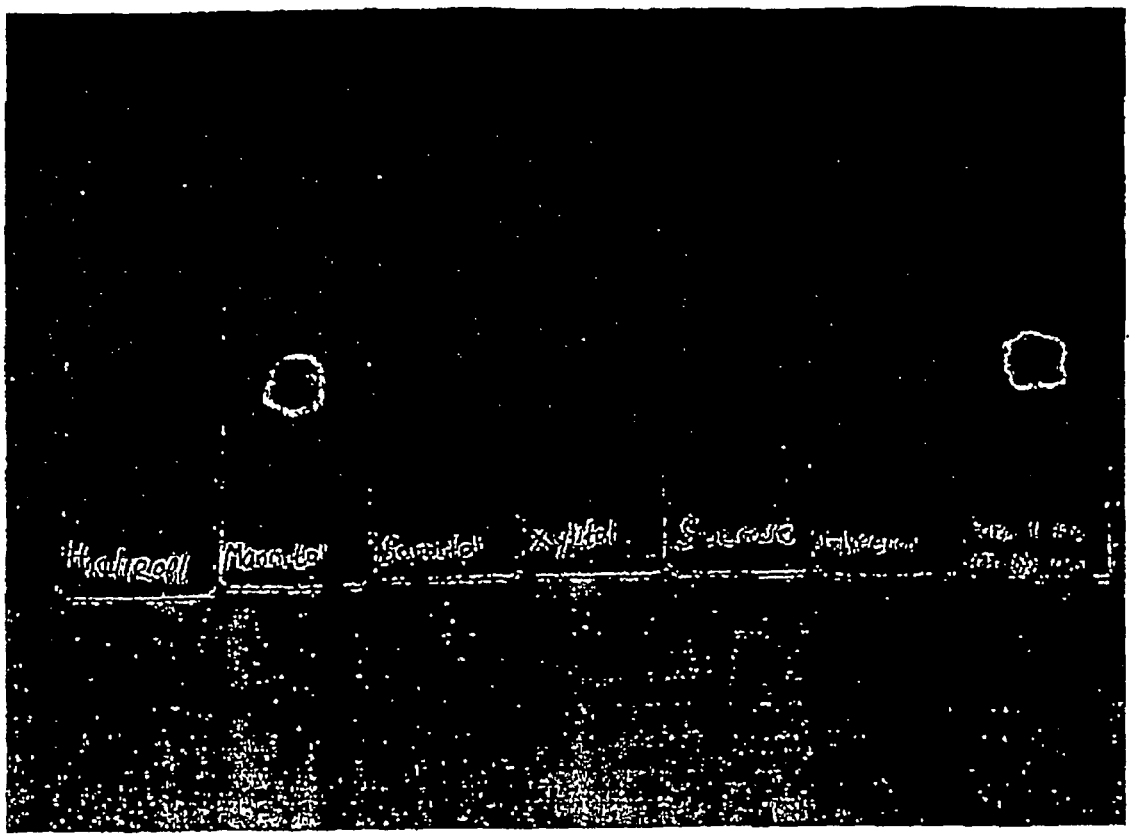
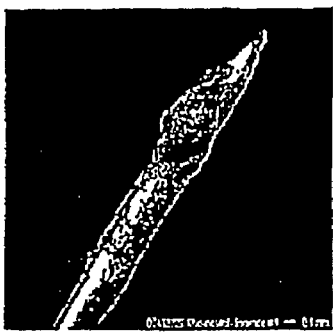
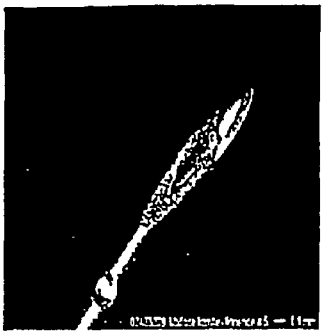


FIGURE 2

FIGURE 3



Myo-inositol



Maltose

Glycerol

FIGURE 4

Glycine Lactose Mannitol

FIGURE 5

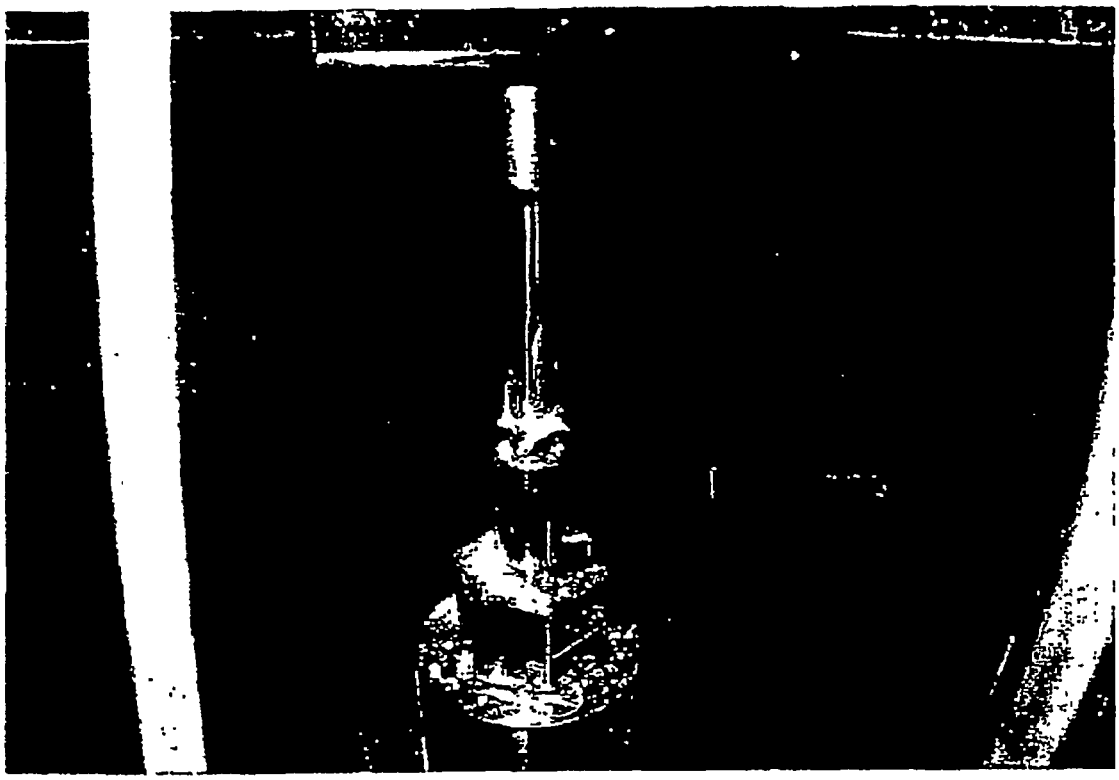


FIGURE 6

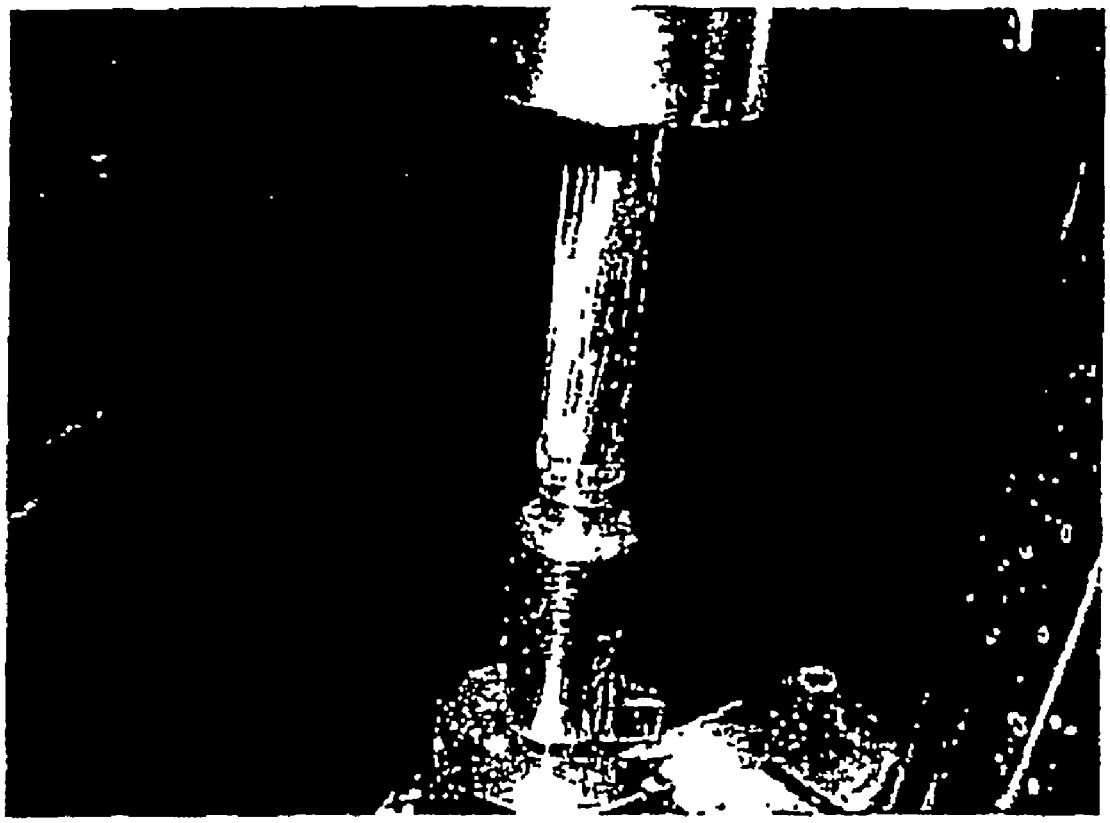
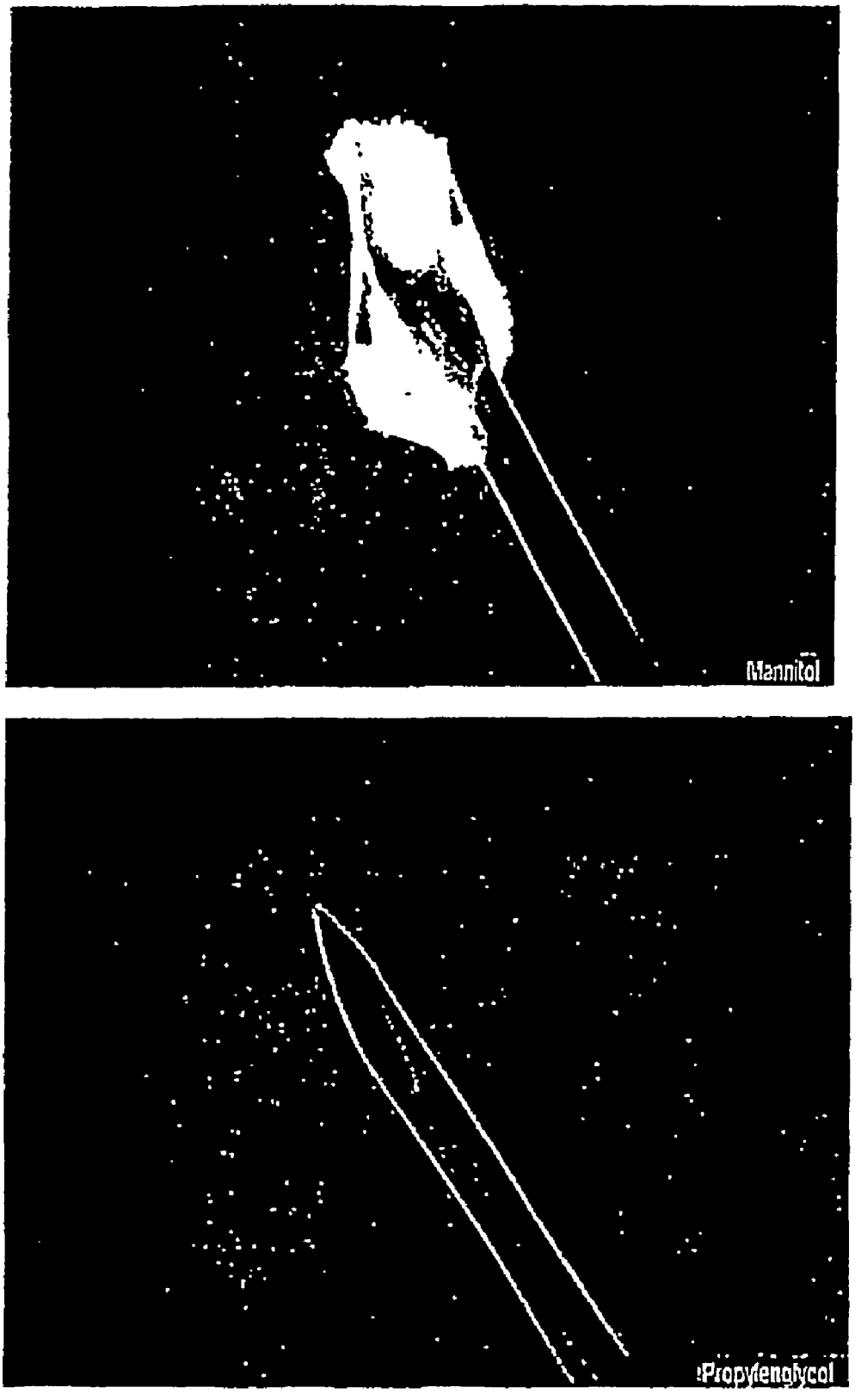


FIGURE 7



PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES

CROSS REFERENCE TO RELATED APPLICATIONS

This Application is a continuation of International Application serial no. PCT/DK2004/000792 filed Nov. 18, 2004 and claims priority from U.S. application Ser. No. 60/524,653 filed Nov. 24, 2003 and from Danish Application serial no. PA 2003 01719 filed Nov. 20, 2003.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated. The present invention further relates to methods for reducing the clogging of injection devices by a peptide formulation and for reducing deposits on production equipment during production of a peptide formulation.

BACKGROUND OF THE INVENTION

The inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known and one of the more common isotonic agents used in such formulations is mannitol. However, the present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. Such deposits increase the need to clean the filling equipment during production of the formulation and this results in reduced production capability. In addition, such deposits may also result in reduced yield of the final product since vials/cartridges containing the peptide formulation may need to be discarded if particles are present. Finally, the present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

Accordingly, it is desirable to identify an alternative isotonic agent to mannitol for inclusion in peptide-containing formulations and in particular, for inclusion in peptide formulations which are administered by injection.

SUMMARY OF THE INVENTION

The present inventors have discovered that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices. The present compositions may be formulated with any peptide and are also physically and chemically stable thus rendering them shelf-stable and suitable for invasive (e.g. injection, subcutaneous injection, intramuscular, intravenous or infusion) as well as non-invasive (e.g. nasal, oral, pulmonary, transdermal or transmucosal e.g. buccal) means of administration.

The present invention therefore relates to a pharmaceutical formulation comprising a peptide and propylene glycol, where the propylene glycol is present in a concentration of 1-100 mg/ml and the pH of the formulation is from 7-10. In a preferred embodiment, the pharmaceutical formulations of the invention further contain a buffer and a preservative.

The present invention also relates to methods for producing the pharmaceutical formulations of the invention.

In one embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;

b) adding propylene glycol to the first solution;

c) mixing the first solution with a second solution containing peptide dissolved in water; and

d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;

b) adding the peptide to the solution of step a); and

c) adjusting the pH of the solution of step b) to the desired pH.

The present invention further relates to methods of treatment using the pharmaceutical formulations of the invention where the compositions are administered in an amount effective to combat the disease, condition, or disorder for which administration of the peptide contained in the formulation is indicated.

In addition the present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows a photograph of dried droplets on microscope slides of from left to right, placebo (no peptide) formulations containing no isotonic agent (e only water, preservative and buffer), mannitol, sorbitol, xylitol, sucrose or glycerol as the isotonic agent with the far right slide containing mannitol with peptide Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

FIG. **2** shows light microscopy pictures of from left to right, some of the dried droplets of placebo formulations containing mannitol, arginin, inositol or glycerol as the isotonic agent.

FIG. **3** shows light microscopy pictures of clogged needles dosed with placebo formulations containing myoinositol, maltose or glycerol as the isotonic agent.

FIG. **4** shows light microscopy pictures of deposits on needles dosed with placebo formulations containing glycine, lactose or mannitol as the isotonic agent.

FIG. **5** shows filling equipment after 24 hours simulated filling with Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) medium containing myo-inositol.

FIG. **6** shows deposits on filling equipment after 24 hours simulated filling with a mannitol-containing placebo formulation.

FIG. **7** shows deposits on needles dosed with mannitol (top panel) and propylene glycol (bottom panel)-containing Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical formulation comprising a peptide or a mixture of peptides and propylene glycol where the final concentration of propylene glycol in the formulation is 1-100 mg/ml and the pH of the formulation is in the range of from 7-10.

The pharmaceutical formulations of the invention are found to be optimal for production because they exhibit reduced deposits in production equipment relative to formulations containing other isotonicity agents as measured by the simulated filling studies described in the Examples. In addition, the pharmaceutical formulations of the invention are found to be optimal for use in injection devices because they exhibit reduced clogging of the injection devices relative to formulations containing other isotonicity agents as measured by the simulated in use studies described in the Examples.

The formulations of the present invention may be formulated with any peptide where examples of such peptides include, but are not limited to, glucagon, human growth hormone (hGH), insulin, aprotinin, FactorVII, tissue plasminogen activator (TPA), FactorVIIa, FFR-FactorVIIa, heparinase, ACTH, Heparin Binding Protein, corticotropin-releasing factor, angio-tensin, calcitonin, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, fibroblast growth factors, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods, DPP IV, interleukins, immunoglobulins, complement inhibitors, serine protease inhibitors, cytokines, cytokine receptors, PDGF, tumor necrosis factors, tumor necrosis factors receptors, growth factors and analogues as well as derivatives thereof where each of these peptides constitutes an alternative embodiment of the present invention.

In the present application, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either at the N-terminal end or at the C-terminal end of the parent peptide or both. Typically "an analogue" is a peptide wherein 6 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, more preferably a peptide wherein 3 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, and most preferably, a peptide wherein one amino acid has been substituted and/or added and/or deleted from the parent peptide.

In the present application, "a derivative" is used to designate a peptide or analogue thereof which is chemically modified by introducing an organic substituent e.g. ester, alkyl or lipophilic functionalities, on one or more amino acid residues of the peptide or analogue thereof.

In one embodiment, the peptide to be included in the formulation of the invention is a GLP-1 agonist where "a GLP-1 agonist" is understood to refer to any peptide which fully or partially activates the human GLP-1 receptor. In a preferred embodiment, the "GLP-1 agonist" is any peptide that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal and the insulin concentration measured over time.

Methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 analogues and derivatives which can be used according to the present invention includes those referred to in WO 99/43705 (Novo Nordisk A/S), WO 99/43706 (Novo Nordisk A/S), WO 99/43707 (Novo Nordisk A/S), WO 98/08871 (analogues with lipophilic substituent) and in WO 02/46227 (analogues fused to serum albumin or to Fc portion of an Ig).(Novo Nordisk A/S), WO 99/43708 (Novo Nordisk A/S), WO 99/43341 (Novo Nordisk A/S), WO 87/06941 (The General Hospital Corporation), WO 90/11296 (The General Hospital Corporation), WO 91/11457 (Buckley et al.), WO 98/43658 (Eli Lilly & Co.), EP 0708179-A2 (Eli Lilly & Co.), EP 0699686-A2 (Eli Lilly & Co.), WO 01/98331 (Eli Lilly & Co).

In one embodiment, the GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

In one embodiment, the GLP-1 agonist is a derivative of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, which comprises a lipophilic substituent.

In this embodiment of the invention, the GLP-1 derivative preferably has three lipophilic substituents, more preferably two lipophilic substituents, and most preferably one lipophilic substituent attached to the parent peptide (ie GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue), where each lipophilic substituent (s) preferably has 4-40 carbon atoms, more preferably 8-30

carbon atoms, even more preferably 8-25 carbon atoms, even more preferably 12-25 carbon atoms, and most preferably 14-18 carbon atoms.

In one embodiment, the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In another embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In yet another embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid. Preferably, the lipophilic substituent is an acyl group having the formula $CH_3(CH_2)_nCO$—, wherein n is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $CH_3(CH_2)_{12}CO$—, $CH_3(CH_2)_{14}CO$—,$CH_3(CH_2)_{16}CO$—, $CH_3(CH_2)_{18}CO$—, $CH_3(CH_2)_{20}CO$— and $CH_3(CH_2)_{22}CO$—. In a more preferred embodiment, the lipophilic substituent is tetradecanoyl. In a most preferred embodiment, the lipophilic substituent is hexadecanoyl.

In a further embodiment of the present invention, the lipophilic substituent has a group which is negatively charged such as a carboxylic acid group. For example, the lipophilic substituent may be an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid of the formula $HOOC(CH_2)_mCO$—, wherein m is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $HOOC(CH_2)_{14}CO$—, $HOOC(CH_2)_{16}CO$—, $HOOC(CH_2)_{18}CO$—, $HOOC(CH_2)_{20}CO$— or $HOOC(CH_2)_{22}CO$—.

In the GLP-1 derivatives of the invention, the lipophilic substituent(s) contain a functional group which can be attached to one of the following functional groups of an amino acid of the parent GLP-1 peptide:

(a) the amino group attached to the alpha-carbon of the N-terminal amino acid,
(b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid,
(c) the epsilon-amino group of any Lys residue,
(d) the carboxy group of the R group of any Asp and Glu residue,
(e) the hydroxy group of the R group of any Tyr, Ser and Thr residue,
(f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or
(g) the thiol group of the R group of any Cys residue.

In one embodiment, a lipophilic substituent is attached to the carboxy group of the R group of any Asp and Glu residue.

In another embodiment, a lipophilic substituent is attached to the carboxy group attached to the alpha-carbon of the C-terminal amino acid.

In a most preferred embodiment, a lipophilic substituent is attached to the epsilon-amino group of any Lys residue.

In a preferred embodiment of the invention, the lipophilic substituent is attached to the parent GLP-1 peptide by means of a spacer. A spacer must contain at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the parent GLP-1 peptide.

In one embodiment, the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. For purposes of the present invention, the phrase "a dipeptide such as Gly-Lys" means any combination of two amino acids except Cys or Met, preferably a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and the N-terminal amino acid residue is Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe, Pro, Ser, Tyr, Thr, Lys, His and Trp. Preferably, an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

Preferred spacers are lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, each of which constitutes an individual embodiment. Most preferred spacers are glutamyl and beta-alanyl. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ϵ-amino group of Lys and the lipophilic substituent. In one embodiment, such a further spacer is succinic acid which forms an amide bond with the ϵ-amino group of Lys and with an amino group present in the lipophilic substituent. In another embodiment such a further spacer is Glu or Asp which forms an amide bond with the ϵ-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ϵ}-acylated lysine residue.

In another embodiment, the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent. Preferably, the spacer is succinic acid.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH$—$CO(CH_2)_qCO$—, wherein p is an integer from 8 to 33, preferably from 12 to 28 and q is an integer from 1 to 6, preferably 2.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO$—$NHCH(COOH)(CH_2)_2CO$—, wherein r is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO$—$NHCH((CH_2)_2COOH)CO$—, wherein s is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO$— wherein t is an integer from 6 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula —$NHCH(COOH)(CH_2)_4NH$—$CO(CH_2)_uCH_3$, wherein u is an integer from 8 to 18.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO$—NH—$(CH_2)_z$—CO, wherein v is an integer from 4 to 24 and z is an integer from 1 to 6.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula —$NHCH(COOH)(CH_2)_4NH$—$COCH((CH_2)_2COOH)NH$—$CO(CH_2)_wCH_3$, wherein w is an integer from 10 to 16.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula —$NHCH(COOH)(CH_2)_4NH$—$CO(CH_2)_2CH(COOH)NHCO(CH_2)_xCH_3$, wherein x is zero or an integer from 1 to 22, preferably 10 to 16.

In yet another embodiment the GLP-1 agonist is Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexade-canoyl)))-GLP-1(7-37).

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Gly^8-GLP-1(7-36)-amide, Gly^8-GLP-1(7-37), Val^8-GLP-1(7-36)-amide, Val^8-GLP-1(7-37), Val^8Asp^{22}-GLP-1(7-36)-amide, Val^8Asp^{22}-GLP-1(7-37), Val^8Glu^{22}-GLP-1(7-36)-amide, Val^8Glu^{22}-GLP-1(7-37), Val^8Lys^{22}-GLP-1(7-36)-amide, Val^8Lys^{22}-GLP-1(7-37), Val^8Arg^{22}-GLP-1(7-36)-amide, Val^8Arg^{22}-GLP-1(7-37),

$Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}$-GLP-1(7-37); $Arg^{26,34}Lys^{40}$-GLP-1(7-37); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{22}$-GLP-1(7-37); $Met^{8}Arg^{22}$-GLP-1(7-37); $Gly^{8}His^{22}$-GLP-1(7-37); $Val^{8}His^{22}$-GLP-1(7-37); $Met^{8}His^{22}$-GLP-1(7-37); His^{37}-GLP-1(7-37); Gly^{8}-GLP-1(7-37); Val^{8}-GLP-1(7-37); Met^{8}-GLP-1(7-37); $Gly^{8}Asp^{22}$-GLP-1(7-37); $Val^{8}Asp^{22}$-GLP-1(7-37); $Met^{8}Asp^{22}$-GLP-1(7-37); $Gly^{8}Glu^{22}$-GLP-1(7-37); $Val^{8}Glu^{22}$-GLP-1(7-37); $Met^{8}Glu^{22}$-GLP-1(7-37); $Gly^{8}Lys^{22}$-GLP-1(7-37); $Val^{8}Lys^{22}$-GLP-1(7-37); $Met^{8}Lys^{22}$-GLP-1(7-37); $Gly^{8}Arg^{22}$-GLP-1(7-37); $Val^{8}Lys^{22}His^{37}$-GLP-1(7-37); $Gly^{8}Glu^{22}His^{37}$-GLP-1(7-37); $Val^{8}Glu^{22}His^{37}$-GLP-1(7-37); $Met^{8}Glu^{22}His^{37}$-GLP-1(7-37); $Gly^{8}Lys^{22}$ His^{37}-GLP-1(7-37); $Met^{8}Lys^{22}His^{37}$-GLP-1(7-37); $Gly^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Val^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Met^{8}Arg^{22}His^{37}$-GLP-1(7-37); $Gly^{8}His^{22}His^{37}$-GLP-1(7-37); $Val^{8}His^{22}His^{37}$-GLP-1(7-37); $Met^{8}His^{22}His$ ^{37}-GLP-1(7-37); $Gly^{8}His^{37}$-GLP-1(7-37); $Val^{8}His^{37}$-GLP-1(7-37); $Met^{8}His^{37}$-GLP-1(7-37); $Gly^{8}Asp^{22}His^{37}$-GLP-1(7-37); $Val^{8}Asp^{22}His^{37}$-GLP-1(7-37); $Met^{8}Asp^{22}His^{37}$-GLP-1(7-37); Arg^{26}-GLP-1(7-36)-amide; Arg^{34}-GLP-1(7-36)-amide; Lys^{36}-GLP-1(7-36)-amide; $Arg^{26,34}Lys^{36}$-GLP-1(7-36)-amide; $Arg^{26,34}$-GLP-1(7-36)-amide; $Arg^{26,34}Lys^{40}$-GLP-1(7-36)-amide; $Arg^{26}Lys^{36}$-GLP-1(7-36)-amide; $Arg^{34}Lys^{36}$-GLP-1(7-36)-amide; Gly^{8}-GLP-1(7-36)-amide; Val^{8}-GLP-1(7-36)-amide; Met^{8}-GLP-1(7-36)-amide; $Gly^{8}Asp^{22}$-GLP-1(7-36)-amide; $Gly^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}Asp^{22}$-GLP-1(7-36)-amide; $Met^{8}Asp^{22}$-GLP-1(7-36)-amide; $Gly^{8}Glu^{22}$-GLP-1(7-36)-amide; $Val^{8}Glu^{22}$-GLP-1(7-36)-amide; $Met^{8}Glu^{22}$-GLP-1(7-36)-amide; $Gly^{8}Lys^{22}$-GLP-1(7-36)-amide; $Val^{8}Lys^{22}$-GLP-1(7-36)-amide; $Met^{8}Lys^{22}$-GLP-1(7-36)-amide; $Gly^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}Arg^{22}$-GLP-1(7-36)-amide; $Val^{8}Arg^{22}$-GLP-1(7-36)-amide; $Met^{8}Arg^{22}$-GLP-1(7-36)-amide; $Gly^{8}His^{22}$-GLP-1(7-36)-amide; $Val^{8}His^{22}$-GLP-1(7-36)-amide; $Met^{8}His^{22}$-GLP-1(7-36)-amide; His^{37}-GLP-1(7-36)-amide; $Val^{8}Arg^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Arg^{37}$-GLP-1(7-36)-amide; $Gly^{8}His^{37}$-GLP-1(7-36)-amide; $Val^{8}His^{37}$-GLP-1(7-36)-amide; $Met^{8}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}Asp^{22}$ His^{37}-GLP-1(7-36)-amide; $Val^{8}Asp^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Asp^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Glu^{22}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}Lys^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}Lys^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}Lys^{22}His^{37}$-GLP-1(7-36)-amide; $Gly^{8}Arg^{22}His^{37}$-GLP-1(7-36)-amide; $Val^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; $Met^{8}His^{22}His^{37}$-GLP-1(7-36)-amide; and derivatives thereof.

In yet another embodiment the GLP-1 agonist is selected from the group consisting of $Val^{8}Trp^{19}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}$-GLP-1(7-37), $Val^{8}Tyr^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Leu^{16}Glu^{22}$-GLP-1(7-37), $Val^{8}Tyr^{18}Glu^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}$ His^{37}-GLP-1(7-37), $Val^{8}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Ile^{33}$-GLP-1(7-37), $Val^{8}Glu^{22}Val^{25}Ile^{33}$-GLP-1(7-37), $Val^{8}Trp^{16}Glu^{22}Val^{25}$-GLP-1(7-37), analogues thereof and derivatives of any of these.

In yet another embodiment the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue or a derivative of any of these.

Examples of exendins as well as analogues, derivatives, and fragments thereof to be included within the present invention are those disclosed in WO 97/46584, U.S. Pat. No. 5,424,286 and WO 01/04156. U.S. Pat. No. 5,424,286 describes a method for stimulating insulin release with an exendin polypeptide. The exendin polypeptides disclosed include HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGX;
wherein X=P or Y, and HX1X2GTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS;
wherein X1X2=SD (exendin-3) or GE (exendin-4)). WO 97/46584 describes truncated versions of exendin peptide(s). The disclosed peptides increase secretion and biosynthesis of insulin, but reduce those of glucagon. WO 01/04156 describes exendin-4 analogues and derivatives as well as the preparation of these molecules. Exendin-4 analogues stabilized by fusion to serum albumin or Fc portion of an Ig are disclosed in WO 02/46227.

In one embodiment, the exendin-4 analogue is HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSS-GAPPSKKKKKK-amide.

Where the peptide to be included in the formulation of the invention is a GLP-1 agonist, the GLP-1 agonist is present in a concentration from about 0.1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 50 mg/ml, and most preferably in a concentration of from about 0.1 mg/ml to about 10 mg/ml.

In another embodiment, the peptide to be included in the formulation of the invention is insulin, where "insulin" is understood to mean human insulin, [where "human insulin" means insulin having the amino acid sequence shown in DSHW Nicol and L F Smith: *Nature,* (1960) 4736:483-485, which is hereby incorporated by reference], human insulin analogs, human insulin derivatives or mixtures thereof, where examples of insulin analogs and derivatives are those disclosed in EP 0 792 290 (Novo Nordisk A/S), EP 0 214 826 and EP 0 705 275 (Novo Nordisk A/S), U.S. Pat. No. 5,504,188 (Eli Lilly), EP 0 368 187 (Aventis), U.S. Pat. Nos. 5,750,497 and 6,011,007, EP 375437 and EP 383472 and where such insulins may include, but are not limited to, NPH insulin, Lys β29 (Nε-tetradecanoyl) des(B30) human insulin, Lys^{B29}-(N^{ϵ}-(γ-glutamyl-N^{α}-lithocholyl) des(B30) human insulin, N^{LB29}-octanoyl insulin, 30/70 mixtures of prompt insulin zinc (SEMILENTE®) with extended insulin zinc (ULTRALENTE®), sold commercially as LENTE®, insulin glargine (LANTUS®) or extended insulin zinc (ULTRALENTE®), Lys^{B28} Pro^{B29} human insulin (HUMALOG®), Asp^{B28} human insulin, insulin aspart (NOVOLOG®), or a 30/70 mixture of insulin aspart and insulin aspart protamine (NOVOMIX®).

In one embodiment, the insulin is a derivative of human insulin or a human insulin analogue where the derivative contains at least one lysine residue and a lipophilic substituent is attached to the epsilon amino group of the lysine residue.

In one embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B28 of the insulin peptide.

In an alternative embodiment, the lysine residue to which the lipophilic substituent is attached is present at position B29 of the insulin peptide.

In yet another embodiment, lipophilic substituent is an acyl group corresponding to a carboxylic acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group, branched or unbranched, which corresponds to a carboxylic acid having a chain of carbon atoms 8 to 24 atoms long.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a fatty acid having at least 6 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 6 to 24 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 8 to 12 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an acyl group corresponding to a linear, saturated carboxylic acid having from 10 to 16 carbon atoms.

In another preferred embodiment, the lipophilic substituent is an oligo oxyethylene group comprising up to 10, preferably up to 5, oxyethylene units.

In another preferred embodiment, the lipophilic substituent is an oligo oxypropylene group comprising up to 10, preferably up to 5, oxypropylene units.

In one preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions may be bound to each insulin hexamer with the proviso that when B30 is Thr or Ala and A21 and B3 are both Asn, and Phe^{B1} is not deleted, then 2-4 Zn^{2+} ions are bound to each hexamer of the insulin derivative.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys, with the proviso that if the B30 amino acid residue is Ala or Thr, then at least one of the residues A21 and B3 is different from Asn; Phe^{B1} may be deleted; and the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms.

In another preferred embodiment, the invention relates to a human insulin derivative in which the B30 amino acid residue is deleted or is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; the A21 and the B3 amino acid residues are, independently, any amino acid residues which can be coded for by the genetic code except Lys, Arg and Cys; Phe^{B1} may be deleted; the □-amino group of Lys^{B29} has a lipophilic substituent which comprises at least 6 carbon atoms; and 2-4 Zn^{2+} ions are bound to each insulin hexamer.

Where the peptide to be included in the formulation of the invention is an insulin, the insulin is present in a concentration from about 0.5 mg/ml to about 20 mg/ml, more preferably in a concentration from about 1 mg/ml to about 15 mg/ml.

In another embodiment, the peptide to be included in the formulations of the invention is hGH or Met-hGH.

Where the peptide to be included in the formulation of the invention is hGH or Met-hGH, the hGH or Met-hGH is present in a concentration from about 0.5 mg/ml to about 50 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet another embodiment, the peptide to be included in the formulations of the invention is GLP-2 or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is GLP-2 or an analogue or derivative thereof, the GLP-2 or an analogue or derivative thereof is present in a concentration from about 1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 1 mg/ml to about 10 mg/ml.

In yet a further embodiment, the peptide to be included in the formulations of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof.

Where the peptide to be included in the formulation of the invention is Factor VII or Factor VIIa or an analogue or derivative thereof, the Factor VII or Factor VIIa or an analogue or derivative thereof is present in a concentration from about 0.1 mg/ml to about 10 mg/ml, more preferably in a concentration from about 0.5 mg/ml to about 5 mg/ml.

In one embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 1 to about 50 mg/ml.

In another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 5 to about 25 mg/ml.

In yet another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 8 to about 16 mg/ml.

In yet a further embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13 to about 15 mg/ml.

In still another embodiment, the final concentration of propylene glycol in the formulations of the invention is from about 13.5 to about 14.5 mg/ml.

In another embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 9.5 where the term "about" as used in connection with pH means + or −0.1 pH units from the stated number.

In a further embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the formulation has a pH in the range from about 7.2 to about 8.0.

In a further embodiment of the invention, the formulation has a pH in the range from about 7.0 to about 8.3.

In yet a further embodiment of the invention, the formulation has a pH in the range from about 7.3 to about 8.3.

In a preferred embodiment of the invention, the formulations contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

Where a buffer is to be included in the formulations of the invention, the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof.

Where a pharmaceutically acceptable preservative is to be included in the formulations of the invention, the preservative is selected from the group consisting of phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. Each one of these specific preservatives constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the preservative is phenol or m-cresol.

In a further embodiment of the invention the preservative is present in a concentration from about 0.1 mg/ml to about 50 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 25 mg/ml, and most preferably in a concentration from about 0.1 mg/ml to about 10 mg/ml

The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a chelating agent where the chelating agent may be selected from salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. Each one of these specific chelating agents constitutes an alternative embodiment of the invention.

In a further embodiment of the invention the chelating agent is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1 mg/ml to 2 mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2 mg/ml to 5 mg/ml.

The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995.

In a further embodiment of the invention the formulation may further comprise a stabilizer selected from the group of high molecular weight polymers or low molecular compounds where such stabilizers include, but are not limited to, polyethylene glycol (e.g. PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (e.g. sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof. Each one of these specific stabilizers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the stabilizer is selected from the group consisting of L-histidine, imidazole and arginine.

In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1 mg/ml to 50 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 5 mg/ml to 10 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0 mg/ml to 20 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 20 mg/ml to 30 mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 30 mg/ml to 50 mg/ml.

In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1 mg/ml to 50 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1 mg/ml to 5 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 5 mg/ml to 10 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 10 mg/ml to 20 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 20 mg/ml to 30 mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 30 mg/ml to 50 mg/ml.

The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995.

In a further embodiment of the invention the formulation of the invention may further comprise a surfactant where a surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, e.g. Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glycerolglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quaternary ammonium bases) (e.g. cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives—(e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (e.g. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative embodiment of the invention.

The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995.

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences,* 1985 or in Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995, where

such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

As mentioned above, in a preferred embodiment, the formulations of the invention-contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

In one embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the peptide in water;

c) mixing the first and second solutions; and

d) adjusting the pH of the mixture in c) to the desired pH.

In another embodiment, the method for preparing such a peptide formulation comprises:

a) preparing a first solution by dissolving preservative and buffer in water;

b) adding propylene glycol to the first solution;

c) mixing the first solution with a second solution containing peptide dissolved in water; and

d) adjusting the pH of the mixture in c) to the desired pH.

In yet another embodiment, the method for preparing a peptide formulation comprises:

a) preparing a solution by dissolving preservative, buffer and propylene glycol in water;

b) adding the peptide to the solution of step a); and

c) adjusting the pH of the solution of step b) to the desired pH.

As the formulations of the invention are optimal for production and for use in injection devices since they exhibit reduced deposits of production equipment and reduced clogging of injection devices, the above methods of production can be used to produce peptide formulations suitable for use in production and/or for use in injection devices.

The formulations of the invention are suitable for administration to a mammal, preferably a human. The route of administration of the formulations of the invention may be any route which effectively transports the peptide contained in the formulation to the appropriate or desired site of action, such as oral, nasal, buccal, pulmonal, transdermal or parenteral.

Due to the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular, in a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump.

A further option is a composition which may be a powder or a liquid for the administration of the formulation in the form of a nasal or pulmonal spray. As a still further option, the formulation can also be administered transdermally, e.g. from a patch, optionally a iontophoretic patch, or transmucosally, e.g. bucally. The above-mentioned possible ways to administer the formulations of the invention are not to be considered as limiting the scope of the invention.

Of course, it is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. One skilled in the art would understand that when used in such methods of treatment, the formulations would have to be administered in amount effective to treat the condition or disease for which the peptide was being administered where an "effective amount" or an "amount . . . effective" is understood to mean a dosage which is sufficient in order for the treatment of the patient with the disease or condition to be treated to be effective compared to treatment without the administered dosage. It is to be understood that "an effective amount" is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

The present invention also relates to a method for reducing deposits on production equipment during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.3.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.3 to about 8.3.

The present invention also relates to a method for reducing deposits in the final product during production of a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.3.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.3 to about 8.3.

The present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.

In one embodiment, the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study as described in the Examples.

In another embodiment, the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

In a further embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 1 to about 50 mg/ml.

In another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 5 to about 25 mg/ml.

In yet another embodiment, the isotonicity agent previously utilized in said formulation is replaced with propylene glycol in a concentration of from about 8 to about 16 mg/ml.

In another embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 9.5.

In a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from about 7.0 to about 8.0.

In yet a further embodiment of the invention, the propylene glycol-containing formulation has a pH in the range from 7.2 to about 8.0.

All scientific publications and patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

Example 1

As laboratory experiments have shown that with regards to clogging of needles and deposits on needles, formulations without peptide ("placebo") give the same conclusions as formulations with peptide at 0.3-5.0 mg/ml, the screening studies in Example 1 have been done using placebo except where indicated otherwise.

Preparation of Formulations with Different Isotonic Agents

Preservative (5.5 mg/ml phenol) and buffer 1.24 mg/ml disodium hydrogen phosphate, dihydrate) were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to pH 7.9 using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 μm filter. The isotonic agents tested in each formulation and their concentrations are shown in Table 1.

TABLE 1

Composition of the tested formulations

Formulation no.	Tonicity modifier
1	Glucose monohydrate (38.0 mg/ml)
2	Laktose monohydrate (65.0 mg/ml)
3	Maltose (67.2 mg/ml)
4	Glycine (15.1 mg/ml)
5	Polyethylenglycol 400 (77.5 mg/ml)
6	L-arginin (24.6 mg/ml)
7	Myo-Inositol (35.2 mg/ml)
8	Propylene glycol (13.7 mg/ml)
9	Dimethylsulfon (18 mg/ml)
10	Mannitol (35.9 mg/ml)
11	Sorbitol (39.5 mg/ml)
12	Xylitol (39.5 mg/ml)
13	Sucrose (79.1 mg/ml
14	Glycerol (16 mg/ml)

Osmolarity

The osmolarity of the different placebo formulations was determined and the results are shown in Table 2.

An isotonic solution has an osmolarity of around 0.286 osmol/L. As can be seen from Table 2 three of the formulations (PEG 400, sucrose and xylitol) are more than 20% from being isotonic (0.229-0.343 osmol/l), however for these kind of experiments the osmolarity is not expected to influence the results, though, the tonicity of the formulations should be adjusted in future experiments.

TABLE 2

The measured osmolarity of the formulations

Formulation no.	Isotonic agent	Osmolarity
1	Glucose monohydrate (38.0 mg/ml)	0.315
2	Laktose monohydrate (65.0 mg/ml)	0.283
3	Maltose (67.2 mg/ml)	0.306
4	Glycine (15.1 mg/ml)	0.286
5	Polyethylenglykol 400 (77.5 mg/ml)	0.370
6	L-arginin(24.6 mg/ml)	0.318
7	Myo-Inositol (35.2 mg/ml)	0.285
8	Propylene glycol (13.7 mg/ml)	0.268
9	Dimethylsulfon (18 mg/ml)	0.274
10	Mannitol (35.9 mg/ml)	0.284
11	Sorbitol (39.5 mg/ml)	0.310
12	Xylitol (39.5 mg/ml)	0.351
13	Sucrose (79.1 mg/ml	0.346
14	Glycerol (16 mg/ml)	0.262

Drop Test

A droplet of each formulation is placed on a microscope slide and let to dry. The deposit is visually examined by eye and light microscope.

A photograph of the dried droplets of some of the formulations is shown in FIG. **1**. In this figure it is clearly observed that mannitol cause deposits on the microscope slide when let

to dry. No deposits were observed for sorbitol, xylitol, sucrose and glycerol. The droplet on the far right (Form 1) contains mannitol and Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

In FIG. **2** the candidates causing the most deposits on the microscope slide are shown. For comparison glycerol, which does not cause deposits, is shown (mannitol, arginine, inositol).

Clogging Test

In this test 10 NOVOPENS® 1.5 ml mounted with NOVOFINE 30® G (G 30 needle) were tested for each formulation, 5 of them placed in upright and 5 in horizontal position. The Pensystems were stored at room temperature in between testing. Each day the needle was examined for deposits and an air shot was performed prior to injection into a tissue. Degree of resistance and clogging, if any, was noted. Injections were made on a daily basis with the same needle, and this was done for 9 working days for all the formulations.

The results from the clogging test are shown in Table 3.

TABLE 3

Clogging test in NovoPen 1.5 using 30G NovoFine

Isotonic agent (no. of observations)	Some resistance	Resistance	Much resistance	Clogged	Drop at top of needle	Dried drop at needle top	Gel-like drop on needle	Deposits on needle
Mannitol (90)	10	0	0	0	0	2	0	43
Glycerol (90)	13	0	0	0	1	0	3	0
Sucrose (90)	23	0	0	0	0	0	21	0
Propylene glycol (90)	20	0	0	0	0	0	0	0
PEG 400 (90)	25	1	0	0	12 (5 at needle)	0	0	0
arginin (90)	26	2	0	0	3 (2 at needle)	1	0	0
Xylitol (90)	14	0	0	0	5	0	0	0
Dimethylsulfon (90)	21	0	0	0	4	0	0	0
sorbitol (90)	12	0	0	0	9	1	0	1
Myo-inositol (90)	20	1	2	6	6	0	0	47
Glucose (90)	32	11	5	0	16 (7 at needle)	1	0	(1 at needle)
glycine (90)	41	9	2	0	1 (2 at needle)	0	0	31 (2 at needle)
maltose (90)	35	8	7	4	16 (6 at needle)	0	0	1 (5 at needle)
laktose (90)	44	10	8	0	5	0	0	31 (2 at needle)

In Table 3 and in FIG. **3** it was observed that inositol and maltose clogged the needle. For comparison glycerol which does not clog the needle is shown in FIG. **3**. In FIG. **4**, and in Table 3, it was observed that formulations containing glycine, lactose and mannitol gave rise to a lot of deposits on the needle. For glycine, the deposits were a droplet deposited down the needle, whereas for lactose and mannitol the deposits occurred at the top of the needle.

Simulated Filling

1 L of each formulation was subjected to a simulated filling experiment which lasted for 24 hours. After 24 hours the filling equipment was inspected for the presence of deposits.

Based on the results from the simulated filling studies (data not shown), the placebo formulations can be divided into three categories. 1. Those isotonic agents that do not cause deposits on the filling equipment: Xylitol, glycerol, glucose monohydrate, maltose, PEG 400 and propylene glycol. 2. Those isotonic agent that cause few deposits and have superior filling properties compared to mannitol: Sorbitol, sucrose and glycine. 3. Those isotonic agent that are comparable or worse than mannitol: Mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

Conclusion

In the simulated filling experiment xylitol, glycerol, glucose, maltose, PEG 400, propylene glycol, sorbitol, sucrose and glycine were found to be suitable replacements candidates for mannitol. However, as glucose is a reducing saccharide, and therefore is able to initiate unwanted degradation in the formulation, this tonicity modifier is ruled out. Furthermore, maltose is ruled out due to clogging of needles. This leads to the following candidates: glycerol, xylitol, sorbitol, sucrose, glycine, propylene glycol and PEG 400, which are found to have suitable properties as replacements candidates for mannitol in peptide formulations with regards to drop test, clogging of needles and simulated filling.

However, on the basis of the following considerations, propylene glycol was chosen as the isotonic agent over the other candidates to be further investigated in head to head comparison studies with mannitol:

a. propylene glycol was observed to have no influence on the physical and chemical stability of Arg^{34}, $Lys^{26}(N^{\epsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations;
b. propylene glycol was observed to have no influence on antimicrobial preservative testing; and
c. use of propylene glycol would no require that further toxicity studies be tested

Example 2

Comparison of Mannitol and Propylene Glycol-Containing Placebo Formulations in Simulated Filling Studies and Simulated Use Studies

Preparation of Formulations

Preservative and buffer were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to the aimed pH using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 μm filter. The compositions of the formulations were as follows:

Disodium hydrogen phosphate, dihydrate: 1.42 mg/ml
Phenol: 5.5 mg/ml
Propylene glycol or mannitol: 13.7 or 35.9 mg/ml
Water for Injection: up to 1.0 ml.
pH: 7.90

Simulated Filling Study

A simulated filling study lasting 24 hours was performed as described in Example 1 and after 24 hours, the filling equipment was inspected for the presence of deposits. No deposits were observed on the filling equipment for the propylene glycol formulation. By comparison, after 24 hours, a lot of deposits were observed on the filling equipment for the mannitol formulation (see FIG. **6**).

Simulated in Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1. The same needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. FIG. **7** shows photographs of needles dosed with the propylene glycol (top panel) or mannitol (bottom panel) containing formulations. Deposits on the needle were observed in 48% of the cases when mannitol was used as an isotonic agent whereas no deposits were observed when propylene glycol was used as the isotonic agent.

Example 3

Comparison of Propylene Glycol to Mannitol in Arg^{34}, Lys^{26} (N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) Containing Formulations

Preparation of Formulations

Preservative, isotonic agent (mannitol or propylene glycol) and buffer were dissolved in water and pH was adjusted to the desired pH. Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) was dissolved in water while stirring slowly. The two solutions were then mixed and pH adjusted to the desired pH using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was filtered through a 0.22 μm filter. The compositions of the formulations were as follows:

Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) (6.25 mg/ml),
Disodium hydrogen phosphate, dihydrate (1.42 mg/ml),
Phenol (5.5 mg/ml),
mannitol or propylene glycol (35.9 or 14.0 mg/ml),
Water for Injection (up to 1.0 ml),
pH: 8.15

Simulated in Use Study

For the simulated in use study, a clogging test was conducted as described in Example 1 except that a G31 needle was used. The same G31 needle was used during the study period of ten working days and each day, the needle was inspected for the presence of deposits. FIG. **7** shows photographs of needles with no deposits when dosed with the propylene glycol (bottom panel) or showing deposits when dosed with the mannitol (top panel) containing formulations.

For the mannitol containing formulation, clogging of the needle was observed in 1 out of 10 cases on day 4, 2 out of 10 cases on day 5, 3 out of 10 cases on day 8 and 4 out of 10 cases on day 9. By comparison, no clogging of needles was observed for the propylene glycol containing formulation.

It is believed that similar results to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90. In addition, additional formulations which could be tested include those having the following compositions:

Buffering agents: glycylglycine (1.32 mg/ml), L-Histidine (1.55 mg/ml), Hepes (2.38 mg/ml), or bicine (1.63 mg/ml)

Preservatives: phenol (5.0 or 5.5 mg/ml), benzylalcohol (18 mg/ml) or a mixture of m-cresol and phenol (2.5/2.0 mg/ml)

Propylene glycol: 14.0 or 14.3 mg.ml
Water for injection: up to 1.0 ml
pH: 7.40, 7.70, 7.90 or 8.15

Example 4

Influence of Peptide Concentration on Clogging of Needles

Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations were prepared as described in Example 3 using peptide concentrations ranging from 0-5 mg/ml of Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37). The compositions of the formulations were as follows:

Liraglutide: 0, 0.3, 3 and 5 mg/ml
Disodium hydrogen phosphate, dihydrate: 0.71 mg/ml
Sodium dihydrogenphosphate, dihydrate: 0.62 mg/ml
Mannitol: 36.9 mg/ml
Phenol: 5.0 mg/ml
Water for injection: up to 1.0 ml
pH 7.40

A simulated in use study was conducted as in Example 3 except that a G30 needle was used and the results (data not shown) indicated that the clogging effect of the mannitol-containing formulations relative to the absence of clogging with the propylene glycol formulations was observed independent of the peptide concentration.

Example 5

Clogging of Needles in Lys β29 (Nε-tetradecanoyl) des(B30) Human Insulin and NovoMix 30 Formulations Containing Mannitol

Preparation Of Formulations

The Lys β29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation was prepared as follows:

a) Prepared a first solution by dissolving buffer, sodium chloride, preservatives (phenol and m-cresol) and mannitol in water

b) Prepared a second solution of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and zinc acetate dissolved in water

c) added the peptide-containing solution of step b) to the solution of step a); and

d) adjusted the pH of the solution to the desired pH

The composition of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin-containing formulation prepared in the above manner was as follows:

Lys β29 (Nε-tetradecanoyl) des(B30) human insulin (2400 nmol), Phenol (1.80 mg/ml), m-cresol (2.06 mg/ml), Mannitol (30.0 mg/ml), disodiumphosphate, dihydrate (0.890 mg/ml), Sodium chloride (1.17 mg/ml), Zinc acetate (65.4 ug/ml), water for injection (up to 1.0 ml), pH: 7.4

The NOVOMIX® 30-containing formulation was prepared as follows:

a) Prepared a solution by dissolving buffer, sodium chloride, phenol, mannitol and sodium hydroxide in water
b) Prepared a solution of sodium chloride, phenol and mannitol in water
c) Prepared a solution of protamine sulphate in water
d) Prepared a solution of insulin, hydrochloric acid and zinc in water
e) Solutions b), c) and d) were mixed
f) Solution e) was added to the solution of step a)
g) Adjusted the pH of the solution to the desired pH and crystallized at room temperature
h) Prepared a solution by dissolving m-cresol, phenol and mannitol in water
i) Solution h) is added to the crystalline fraction of step g); and
j) Adjusted the pH to the desired pH

The composition of the NOVOMIX® 30-containing formulation prepared in the above manner was as follows:

Insulin aspart (100 units/ml), protamine sulphate (approx. 0.33 mg/ml), phenol (1.50 mg/ml), m-cresol (1.72 mg/ml), mannitol (30.0 mg/ml), disodiumphosphate dihydrate (1.25 mg/ml), sodium chloride (0.58 mg/ml), zinc (19.6 ug/ml), water for injection (up to 1.0 ml), pH: 7.3.

Results

A simulated in use study was conducted as described in Example 3 using G31 needles where 20 needles were investigated for 10 days. The results were as follows: Clogging of needles was observed for Lys β29 (Nε-tetradecanoyl) des (B30) human insulin on day 2 (5%), day 3 (70%) and on day 4 (100%). Clogging of needles for NovoMix 30 was observed on day 3 (5%), day 4 (10%), day 5 (35%), day 6 (40%), day 8 (50%), day 9 (55%) and day 10 (80%). Thus, the effect of mannitol on the clogging of needles is independent of the type of peptide included in the formulations since a comparable clogging effect was observed with Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37), Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30.

Example 6

Testing of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 formulations containing propylene glycol

The preparation and composition of the Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 formulations will be as described in Example 5 except that mannitol will be replaced with a concentration of propylene glycol that assures tonicity. A simulated in use test will then be conducted as described in Example 5.

Based on the fact that the clogging effect of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and NOVOMIX® 30 mannitol-containing formulations was similar to that observed with Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) mannitol-containing formulations, it is believed that the effect of propylene glycol on the clogging effect of Lys β29 (Nε-tetradecanoyl) des(B30) human insulin and NovoMix 30-containing formulations will be similar to that observed with Arg^{34}, Lys^{26}(N^{ϵ}-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37)-containing formulations.

SEQUENCE LISTING

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<223> OTHER INFORMATION: Lysine at position 44 is amidated

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            20                  25                  30

Ser Gly Ala Pro Pro Ser Lys Lys Lys Lys Lys Lys
        35                  40
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The invention claimed is:

1. A pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

2. The formulation according to claim **1**, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

3. The formulation according to claim **1**, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

4. The formulation according to claim **1**, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

5. The formulation according to claim **1**, wherein the pH of said formulation is about 7.0 to about 9.5.

6. The formulation according to claim **1**, wherein the pH of said formulation is about 7.0 to about 8.3.

7. The formulation according to claim 1, wherein the pH of said formulation is about 7.3 to about 8.3.

8. The formulation according to claim 1, further comprising a preservative.

9. The formulation according to claim 8, wherein said preservative is present in a concentration from 0.1 mg/ml to 20 mg/ml.

10. The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.

11. The formulation according to claim 10, wherein said GLP-1 agonist is a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.

12. The formulation according to claim 11, wherein said lipophilic substituent has from 8 to 40 carbon atoms.

13. The formulation according to claim 12, wherein said spacer is an amino acid.

14. The formulation according to claim 13, wherein said GLP-1 agonist is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

15. The formulation according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of Gly^{8}-GLP-1(7-36)-amide, Gly^{8}-GLP-1(7-37), Val^{8}-GLP-1(7-36) amide, Val^{8}-GLP-1(7-37), $Val^{8}Asp^{22}$-GLP-1(7-36)-amide, $Val^{8}Asp^{22}$-GLP-1(7-37), $Val^{8}Glu^{22}$-GLP-1(7-36) -amide, $Val^{8}Glu^{22}$-GLP-1(7-37), $Val^{8}Lys^{22}$-GLP-1(7-36)-amide, $Val^{8}Lys^{22}$-GLP-1(7-37), $Val^{8}Arg^{22}$-GLP-1(7-36)-amide, $Val^{8}Arg^{22}$-GLP-1(7-37), $Val^{8}His^{22}$-GLP-1(7-36)-amide, $Val^{8}His^{22}$-GLP-1(7-37), Arg^{34}GLP-1(7-37), $Arg^{26,34}Lys^{36}$GLP-1(7-36), Arg^{26}GLP-1(7-37), and Gly^{8}, $Arg^{26,34}Glu^{37}Lys^{38}$GLP-1(7-38) and derivatives of any of these.

16. A method of preparing a GLP-1 agonist formulation suitable for use in an injection device, said method comprising preparing a formulation containing a GLP-1 agonist, propylene glycol, a disodium phosphate dihydrate buffer, and a preservative, wherein said propylene glycol is present in a concentration from about 1 mg/ml to about 100 mg/ml, and wherein said formulation has a pH from about 7.0 to about 10.0, and wherein said GLP-1 agonist, said propylene glycol and said buffer and preservative are mixed together to produce said formulation as follows:

a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;

b) preparing a second solution by dissolving the GLP-1 agonist in water;

c) mixing the first and second solutions; and

adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

17. The method according to claim 16, wherein the concentration of propylene glycol is from about 1 mg/ml to about 50 mg/ml.

18. The method according to claim 16, wherein the concentration of propylene glycol is from about 5 mg/ml to about 25 mg/ml.

19. The method according to claim 16, wherein the concentration of propylene glycol is from about 8 mg/ml to about 16 mg/ml.

20. The method according to claim 16, wherein the pH of said formulation is about 7.0 to about 9.5.

21. The method according to claim 16, wherein the pH of said formulation is about 7.0 to about 8.0.

22. The method according to claim 16, wherein the pH of said formulation is about 7.2 to about 8.0.

23. A method for reducing deposits on production equipment during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

24. The method according to claim 23, wherein the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured by a simulated filling experiment.

25. The method according to claim 23, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

26. A method for reducing deposits in the final product during production of a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

27. The method according to claim 26, wherein the reduction in deposits in the final product is measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.

28. The method according to claim 26, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, glycerol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.

29. A method for reducing the clogging of injection devices by a GLP-1 agonist formulation, said method comprising replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml, and wherein said GLP-1 agonist formulation comprises a disodium phosphate dihydrate buffer.

30. The method according to claim 29, wherein the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent is measured in a simulated in use study.

31. The method according to claim 29, wherein the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of inositol, maltose, glycine, lactose and mannitol.

* * * * *

EXHIBIT D

US009265893B2

(12) **United States Patent**
Hansen et al.

(10) **Patent No.: US 9,265,893 B2**
(45) **Date of Patent: Feb. 23, 2016**

(54) **INJECTION BUTTON**

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(73) Assignee: **Novo Nordisk A/S**, Bagsvaerd (DK)

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A61M 5/315 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 5/31585*** (2013.01); ***A61M 5/31511*** (2013.01); *A61M 5/3158* (2013.01)

(58) **Field of Classification Search**
CPC A61M 2005/2013; A61M 5/31541; A61M 5/20; A61M 5/31583; A61M 5/3158
USPC 604/181, 187, 218–231
See application file for complete search history.

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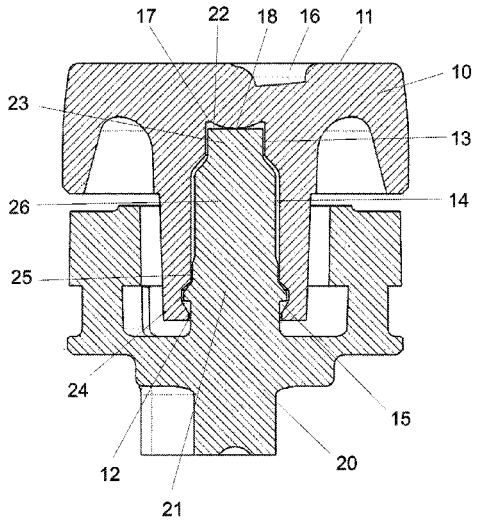
Primary Examiner — Phillip Gray
(74) *Attorney, Agent, or Firm* — Wesley Nicolas

(57) **ABSTRACT**

A push button connection for an injection device comprising a push button (**10**) and a driving part (**20**). The two parts of the push button connection are mounted to each other and is relatively rotatable to each other. In order to minimize the friction occurring between the push button and the driving part when relatively rotated forces are transmitted via a pivot bearing (**18**, **22**). In order also to minimize the effect of forces appearing dislocated from the center line a number of radial bearings (**13**, **23**; **14**, **25**) having a little friction diameter is provided.

6 Claims, 2 Drawing Sheets



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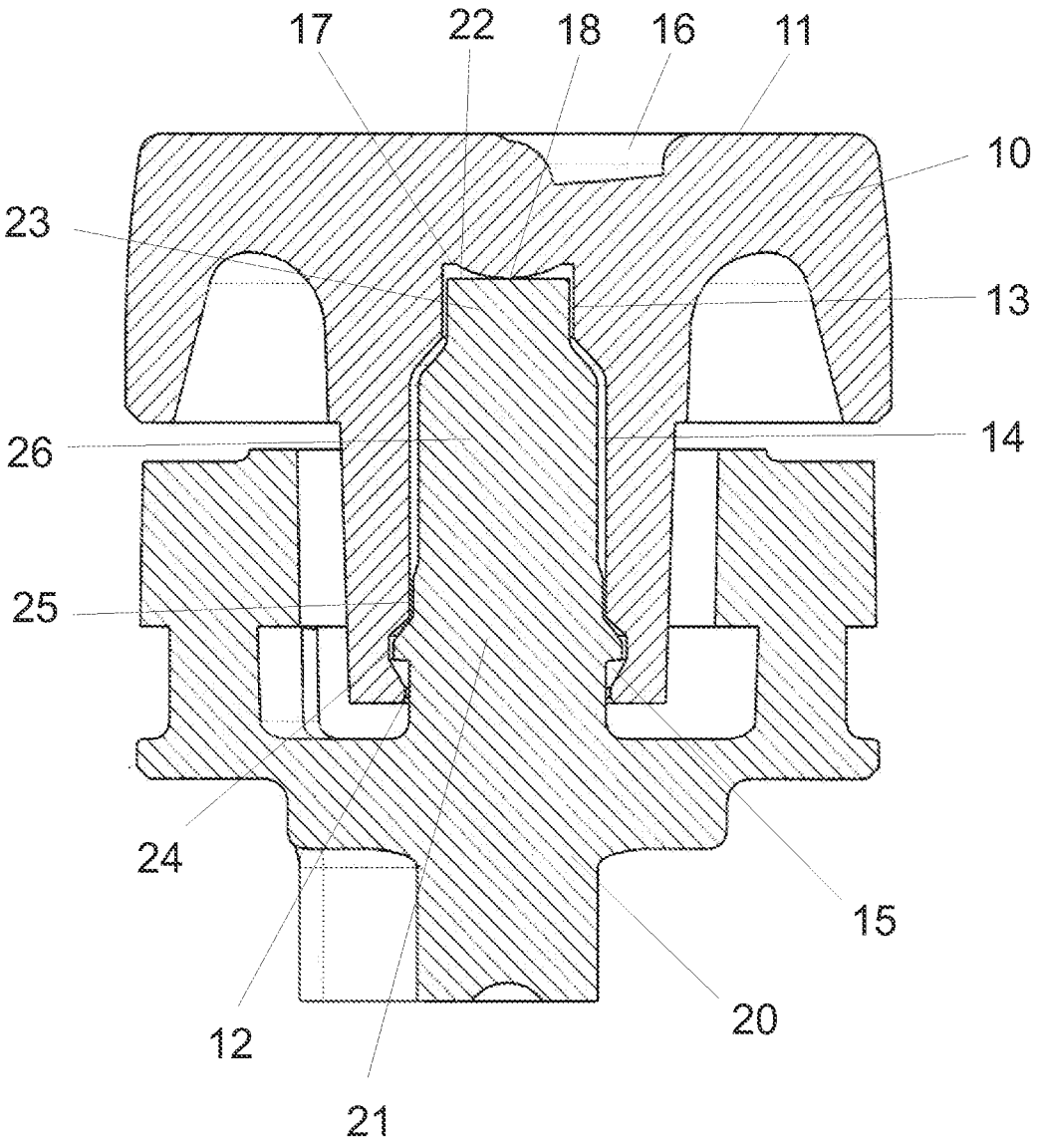

Fig. 1

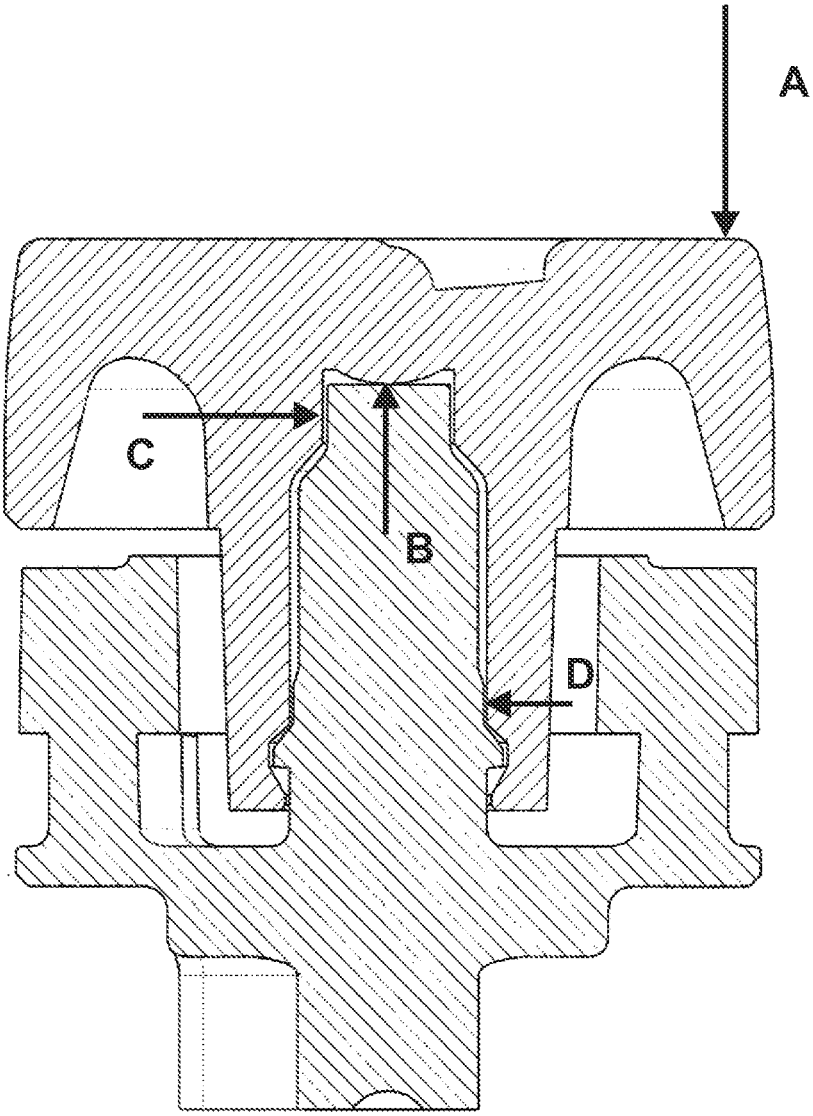

Fig. 2

INJECTION BUTTON

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. §371 national stage application of International Patent Application PCT/EP2008/050624 (published as WO2008/095762), filed Jan. 21, 2008, which claimed priority of European Patent Application 07101729.7, filed Feb. 5, 2007; this application further claims priority under 35 U.S.C. §119 of U.S. Provisional Application 60/899,977, filed Feb. 7, 2007.

THE TECHNICAL FIELD OF THE INVENTION

The invention relates to a push button connection for an injection device and especially to such connection where a push button is rotated relatively to a driving member to which it is connected.

DESCRIPTION OF RELATED ART

U.S. Pat. No. 6,235,004 discloses an injection device in which according to FIG. 15-16 a dose is set by rotating the scale drum out of the housing in a threaded connection. When injecting the set dose the user pushes on the push button which forces the scale drum and the bushing to rotate together back into the housing. During this rotation of the bushing to which the push button is attached, the push button and the bushing rotates relatively to each other. The friction occurring between these relatively rotatable parts contributes to the force a user needs to apply in order to push back the bushing and the scale drum in order to inject the set dose.

U.S. Pat. No. 7,427,275 discloses an injection device in which the push button is formed with a bore encompassing a stem on a sleeve member. The push button and the stem are welded together such that the push button and the sleeve member are axially and rotatably fixed to each other.

DESCRIPTION OF THE INVENTION

It is an object of the present invention to provide a dose button connection for an injection device which minimizes the forces a user must apply to inject a dose.

When a user pushes on the injection button, the force applied is directed to the forward movement of the driving part, however, since the push button and the driving part rotate relatively to each other a friction between these rotating parts will occur. The user therefore also has to apply a force large enough to overcome this friction. One way of minimizing the force a user must apply in order to perform an injection is therefore to minimize this friction. By forming a pivot bearing between the two parts, the surface area of interaction between the two objects can be minimized and the radius of the resulting friction force can be kept at a minimum.

In order to secure the fit between the push button and the driving part and on the same time direct forces applied on the periphery of the push button to the driving part at least one radial bearing between the push button and the protrusion is formed.

Preferably one radial bearing is formed in the upper area and one is formed in the lower area both having the least possible radius of friction. In this way forces applied at in the periphery area of the push button and causing tilting of the push button on the protrusion of the driving part is properly transferred.

If a user applies a force eccentric to the centre axis of the push button i.e. on a peripheral area of the button, the push button will tilt and a reaction torque will occur at the radial bearings. In order to minimize this force pair, which in this load case is located at the distance from the radial bearing surface to the centre axis of the system, this distance, which again equals the radius of the protrusion, must be as little as possible and the distance between the bearings as long as possible. However, in order not to make the protrusion too narrow and fragile it is preferred to balance the radius of the bearings, such that the upper bearing has the smallest diameter and the lower bearing at the root of the column shaped protrusion has a diameter large enough to resist the bending force as a result of the offset applied push button forces.

In order to assemble the push button in an irreversible manner making it difficult to dissemble, it is preferred to secure the push button at the intended position by adding a track into which a rim on the harder part is forced during the manufacture of the injection device. The necessary compliance of the push button for the assembly snap-on can be secured by selection of a soft material and/or a vertical slit in the hollow section of the geometry.

Further the materials used for the push button and the protrusion on the driving part could be materials having low internal friction, or the materials could be surface treated in order to lower the internal friction.

The push button used in the connection has a central bore dedicated to engage the protrusion provided on the driving part. The bottom of the bore is preferable formed with a pivot. This pivot bears on a surface of the protrusion thus forming a pivot bearing.

DEFINITIONS

An "injection pen" is typically an injection apparatus having an oblong or elongated shape somewhat like a pen for writing. Although such pens usually have a tubular cross-section, they could easily have a different cross-section such as triangular, rectangular or square or any variation around these geometries.

As used herein, the term "drug" is meant to encompass any drug-containing flowable medicine capable of being passed through a delivery means such as a hollow needle in a controlled manner, such as a liquid, solution, gel or fine suspension. Representative drugs includes pharmaceuticals such as peptides, proteins (e.g. insulin, insulin analogues and C-peptide), and hormones, biologically derived or active agents, hormonal and gene based agents, nutritional formulas and other substances in both solid (dispensed) or liquid form.

All references, including publications, patent applications, and patents, cited herein are incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

All headings and sub-headings are used herein for convenience only and should not be constructed as limiting the invention in any way.

The use of any and all examples, or exemplary language (e.g. such as) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention. The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

This invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be explained more fully below in connection with a preferred embodiment and with reference to the drawings in which:

FIG. **1** Show a cross section view of the connection between a push button and a driving part.

FIG. **2** Show a cross section view of the connection and the forces occurring.

The figures are schematic and simplified for clarity, and they just show details, which are essential to the understanding of the invention, while other details are left out. Throughout, the same reference numerals are used for identical or corresponding parts.

DETAILED DESCRIPTION OF EMBODIMENT

When in the following terms as "upper" and "lower", "right" and "left", "horizontal" and "vertical", "clockwise" and "counter clockwise" or similar relative expressions are used, these only refer to the appended figures and not to an actual situation of use. The shown figures are schematic representations for which reason the configuration of the different structures as well as there relative dimensions are intended to serve illustrative purposes only.

In that context it may be convenient to define that the term "distal end" in the appended figures is meant to refer to the end of the injection device carrying the injection needle whereas the term "proximal end" is meant to refer to the opposite end pointing away from the injection needle.

FIG. **1** discloses the connection between the push button **10** and the driving part **20**.

When a user wants to inject a dose, which he or she has first selected, the user pushes the push button **10** which then moves the driving part **20** axially forward in the injection device. During this forward movement of the driving part **20** it also rotates usually because it is interfaced with a dose dial drum which is threadedly connected to a housing. Such injection device is described in details in EP 1.003.581. The combined axial and rotatable movement of the driving part **20** drives the set dose out from the injection device.

As the users finger pushes on the push surface **11** of the push button **10** it is unable to rotate due to the friction between the users finger and the push button **10** whereas the driving part **20** is forced to rotate due to its interface, therefore a relative rotation between the push button **10** and the driving part **20** takes place.

The push button **10** which could be manufactured from a suitable polymeric material being softer that the material from which the driving part **20** is manufactured comprises at the proximal end a push surface **11** which is contacted by the user's finger when a dose is to be injected and an opposite located cylindrical bore **12** with a circular cross section. The most proximal part **13** of the bore **12** has a smaller diameter than the remaining part **14** of the bore **12**. At the distal end of the bore **12**, a radial extending track **15** is provided.

The push surface **11** could be provided with a tactile cut-out **16** informing visual impaired users on the content of the injection device and the most proximal bottom surface **17** of the bore **12** is formed with a raised pointer forming a pivot **18**.

The driving part **20** is provided with a protrusion **21** having a circular cross section and a top surface **22**. This protrusion **21** has at its proximal end a top part **23** with a decreased diameter compared to the remaining part **26** of the protrusion **21**. Further the protrusion **21** is provided with a radial extending rim **24** at its distal end. In the area around this rim **24**, the protrusion **21** is provided with a belt **25** with a slightly raised diameter.

When the push button **10** is mounted on the protrusion **21** of the driving element **20** it is simply clicked on such that the extending rim **24** enters the track **15**. This forms a connection almost impossible to disconnect since the polymeric material of the push button **10** is softer than the material from which the protrusion **21** is produced. In this position the pivot **18** formed in the most proximal bottom surface **17** of the bore **12** bears on the top surface **22** of the protrusion **21** thus forming a pivot bearing **22**, **18**. Further the push button **10** is radially supported by the protrusion **21** at the top part **23** forming a radial top bearing **23**, **13**. The belt **25** on the protrusion **21** bears on an area of the remaining part **14** of the bore **12** thus forming a radial bottom bearing **14**, **25**.

In FIG. **2** the push button **10** connection is disclosed with the various forces occurring when a user applies an injection force in the peripheral area of the push button **10**.

When the user applies an injection force A at the peripheral area of the push button **10** a vertical reaction force B will appear at the pivot point **22**, **18**, at the same time a radial force C will occur at the upper radial bearing **13**, **23**. Since the upper radial bearing **13**, **23** are located at the top part **23** having the smaller diameter, the resulting torque is relatively small. Further, a radial force D will occur at the lower radial bearing **14**, **25**, however due to the distance between the upper radial bearing **13**, **23** and the lower radial bearing **14**, **25**, the force resulting on the lower radial bearing **14**, **25** is relatively small.

Some preferred embodiments have been shown in the foregoing, but it should be stressed that the invention is not limited to these, but may be embodied in other ways within the subject matter defined in the following claims.

The invention claimed is:

1. A push button connection for an injection device comprising:

a push button mountable on a driving part being rotatable relatively to the push button and which push button further comprises a bore with a bottom surface and which bore surrounds a protrusion on the driving part which protrusion has a top surface and wherein a pivot bearing is formed between the bottom surface and the top surface, wherein when a user presses on the push button the force is directed toward the driving part and wherein the driving part rotates relative to the push button.

2. A push button connection according to claim **1**, in which at least one radial bearing between the push button and the driving part is provided.

3. A push button connection according to claim **2**, in which an upper radial bearing is provided at a top part of the protrusion and a lower radial bearing is provided at the bottom of the protrusion.

4. A push button connection according to claim **3**, in which the top part of the protrusion accommodating the upper radial bearing has a diameter smaller than the diameter of the remaining part of the protrusion.

5. A push button connection according to claim **1**, in which the push button is manufactured from a polymeric material being softer than the material from which the driving part is manufactured.

6. A push button connection according to claim **1**, in which the protrusion is provided with an extending rim mating with a track provided in the push button.

* * * * *